The New England
Journal of Medicine

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VOLUME 229 OCTOBER 7, 1943 NUMBER 15

THE WORK OF THE MASSACHUSETTS BOARDS OF REGISTRATION IN MEDICINE AND NURSING*

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BOSTON

PREVIOUS to 1942, I knew nothing about boards of registration in medicine and nursing. When I arrived at the State House on a cold morning in February of last year, to find three rooms in which seven clerks and three nurses were busily engaged in a large amount of paper work, I suddenly realized that I was in for it, and I knew that my usual program for the days of the week would have to be materially altered.

To change from a practicing surgeon to the secretary for two such busy boards as the Board of Registration in Medicine and the Board of Registration in Nursing means an alteration in one's entire method of living. To do the work of these boards in addition to the duties of a surgeon is at least time consuming. However, I began to like the work at once because it is important and constructive. It demands honesty above all things; a willingness to co-operate with doctors, laymen, legislators, nurses, educators and even politicians; a sense of justice; and the ability to understand that there are two sides to every question that may arise between physicians and between laymen and physicians. Most of all, it demands a sense of humor. My predecessor had left three vials of aspirin in the office desk. I gave them away, and I have not had any of the promised headaches yet. Perhaps they are just around the corner.

The Board of Registration in Medicine is composed of seven doctors, one of whom is an osteopath, and they come from various parts of the Commonwealth. The governor appoints one member every year, and the term is for seven years. The board elects its own chairman and secretary. Five board members receive $600 per year, the chairman $800, and the secretary $2500. The board meets ten times each year; the secretary visits his office each day that the State House is open for business, and he must spend from one to three hours at the routine of the office. There are seven clerks to handle the work, and two of them are assigned as secretaries to me.

The board gives three examinations each year to candidates for registration. About 600 doctors take them during the twelve months, and most of these are from unapproved schools because the graduates of the approved schools take the examinations given by the National Board of Medical Examiners, which are qualifying in Massachusetts. A candidate must prove that he is the graduate of a legally chartered medical school that has given him one hundred and twenty-eight weeks of medical education. Each board member writes one section of the examination and he corrects his own papers. This is the one tiring feature of the work. Since I give examinations to nurses and attendants as well, I must correct about 2400 papers per year, or approximately seven every day. The examinations last twenty-one hours over a period of three and a half days. Each examiner proctors his own examination. The candidates are known to the board members only by number.

As soon as the notices are sent out that the candidates have passed or failed, I begin to get requests to do something for the unlucky ones. It takes tact and patience to see to it that my relations with the members of the General Court, the families of the candidates and the candidates themselves remain on a friendly basis. When, however, they realize that nothing can be done, that all are treated alike, and that no favors are granted, they appreciate that their only recourse is to take the next examination. Often half those taking the examination are repeaters, and some repeat over a period of fifteen or more years. There is no limit so long as their endurance holds out. Many accusations have been made in the past against board members and the office force that irregularities exist concerning the marks. These have never

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1943.

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been proved, and I doubt that they have had any foundation in fact.

At the board meetings, hearings are conducted to settle the guilt or innocence of registered physicians against whom complaints have been made, or who have been found guilty in the courts. The complaints are usually concerned with negligence or deceit. The doctors who have been found guilty in the courts are those who, in most cases, have violated the federal narcotic law or have performed criminal abortions.

If the doctor is found guilty, his license is suspended or revoked, according to the seriousness of the case. Most of the complaints are handled by the secretary, who decides, after a conference, either that the matter can be settled without a hearing before the full board or that the complaint is not worthy of a hearing.

Complaints against unregistered practitioners of medicine are many and varied; these are turned over to the State Police for investigation. The latter frequently make arrests; the culprits are tried and if found guilty are fined. All that we have to do is to testify that the accused is not registered to practice medicine in the Commonwealth.

One of the duties of the board is to introduce legislation considered essential to the elevation of the standards of the profession, and for the protection of the interests of the people of the Commonwealth. I believe that it is also the duty of the board to oppose legislation that it knows is detrimental to the advance of medicine and the maintenance of its standards.

I have found out during the past year that it is very important at public hearings before a legislative committee to have one's facts well in hand, to be able to present arguments concisely, and not to antagonize the members of the committee. It is of the greatest help to be able to talk to the members of the legislature who may be influential in passing or defeating the legislation. An eagle eye must be kept on the calendar so that important bills may not slip by without the knowledge of the medical profession. One antivivisection bill reached the governor's desk this year without any opposition's having been presented by the profession. Fortunately, in this case, the omission was discovered in time to organize protests that finally brought about the withdrawal of the bill. By hard work and long hours spent on the problems, and with complete co-operation with the Massachusetts Medical Society, the board has been able to defeat two dangerous nursing bills and two antivivisection bills, and now has a bill in committee to continue the control of approved medical schools in this state forever.

Since the process of introducing legislation or defeating unfavorable legislation is a matter that concerns the law, and since physicians are very busy at their daily tasks of caring for the sick, and since physicians generally abhor anything that has to do with politicians and their ways, I believe that it would be for the best interests of this society to employ a legislative counsel to assist the members of the Committee on Legislation and of the Board of Registration in Medicine with such problems. A well-known and astute lawyer who "knows his way around" would be of great help, and I am sure that he would meet with the approval of those legislators who are looking after the interests of the medical profession.

Once a doctor has been registered to practice medicine in this state, he may do so throughout his life unless he is found guilty of gross misconduct. It has been extremely humiliating for our office not to be able to furnish information to the Army, the Navy, the F.B.I., the Committee of Ethics and Discipline of the Massachusetts Medical Society, hospitals, civic groups and individuals concerning doctors whom we have registered. For a small fee and a few minutes' time on the part of the doctors we could make it possible to know the pertinent facts concerning every registered physician in the Commonwealth; every member of this society could have the list in his bookcase; he could be immediately aware of the presence of the unregistered practitioner in his community; and the office of the board could give fairly accurate information to the right people concerning physicians registered in Massachusetts. I have no doubt that this information would have been of considerable help to the various district committees of the Procurement and Assignment Service during the past two years. I am sure that if every registered doctor had to reregister every year on his birthday, the profession as a whole would be benefited. Such legislation has been of great value to the nurses and the dentists.

The secretary of the Board of Registration in Medicine is the chairman of the Approving Authority for Medical Schools; the other two members of that board are the commissioner of education and the commissioner of health. It is the task of the authority under the present law to inspect medical schols at the request of their trustees. As you very likely know, the present law requires that any young man entering medical school after January 1, 1941, must graduate from an approved school in order to be allowed to take the examination for registration in this state. Therefore, after January 1, 1945, the problem of the unapproved medical school in the Common-

wealth will disappear, and Massachusetts will rise to an even rank with the other states. This most excellent piece of legislation was made possible by the combined efforts of the members of this society, the Board of Registration in Medicine and interested legislators.

The failure of the Massachusetts General Court to enact this important legislation earlier produced many difficulties for this society, the medical profession generally and the Board of Registration in Medicine in particular. Although it will take many years to eliminate all the bad results of inferior medical education in Massachusetts, at least we have the pleasure of knowing that the situation is improving constantly and that hereafter we need not be ashamed of our state in this important matter.

The secretary of the Board of Registration in Medicine is also the secretary of the Board of Registration in Nursing, which comprises six physicians and nurses who are leaders in their respective fields, who must shape the destiny of nursing education in the Commonwealth. It is the duty of this board to examine candidates for registration in nursing who are the graduates of any one of the sixty-three approved schools in Massachusetts, and to register those from other states by reciprocity if they meet the educational requirements of our law. These women must be at least twenty-one years of age and must have attended a school of nursing for one thousand and ninety-five days. Here again, each member of the board writes, proctors and corrects his own examination, and the candidates are known only by numbers. Since one does not have to be a registered nurse to work at her profession in Massachusetts there is no monetary value attached to the certificate, and the difficulties met with in the medical profession are not encountered.

The Board of Registration in Nursing also examines those who wish to become licensed attendants. These women must be twenty years of age or over and must have attended a school for the training of practical nurses. After October, 1944, they must be graduated from an approved school for attendants before they can take the examination for a license. Last year we licensed by waiver and examination about 2000 of these valuable women.

The secretary of the Board of Registration in Medicine is also the secretary of the Approving Authority for Nursing Schools. This board is made up of men and women who are on the administrative, executive or teaching staffs of hospitals or nursing schools. They are appointed by the Governor. It is the work of this board to determine the educational qualifications of the prospective nurse, the courses to be taught in the nursing schools and the qualifications of the teachers in the nursing schools. It must determine the quality of the schools in every respect. To inspect the sixty-three approved schools in this state, to help them with their various problems, to try to improve them and to make sure that the quality of our nurses is maintained at a high level are the duties of two supervising nurses employed by our office. These nurses are at the top of their profession, and the success or failure of the work of the approving authority rests, to a great extent, on their shoulders. During this emergency, when there is a shortage of nurses, the approving authority has attempted in every way possible within the law to increase the number of nurses and at the same time to maintain high standards. Their latest act has been to present legislation to the Governor for emergency action whereby nurses may become registered at the age of twenty instead of twenty-one and attendants at the age of nineteen instead of twenty. If this is done, more young women will go into nursing schools as soon as they finish high school, since they will not have to await their eighteenth birthday.

* * *

I have presented an outline of the work of the Board of Registration in Medicine, the Board of Registration in Nursing and their respective approving authorities. All these units are functioning under new laws that promise to work to the advantage of medicine and nursing in the Commonwealth and eventually to bring it into line with the states that have the highest standards. There is no doubt that all this will be to the best interests of the public when they need medical and nursing care. Personally, I have but one aim in all this work: to improve the conditions in private practice and in hospitals that affect the care of patients. Better schools of medicine and nursing mean better physicians and nurses, and that means better care of the sick. The Board of Registration in Medicine is representative of the Massachusetts Medical Society. The board wants to do what you would like to have it do. We are trying at all times to interpret your desires to make the practice of medicine in Massachusetts the very best. We hope for, and expect to get, your co-operation in this vital work.

CARCINOMA OF THE LARYNX*

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IT HAS been estimated that the larynx is involved in from 2 to 5 per cent of all cases of carcinoma. This incidence varies with different authors, since most of the data have been obtained from actuaries and are based on different opinions concerning the primary source of the tumor. Even acceptance of the lowest rate of incidence signifies that the disease is not uncommon. It has likewise been pointed out that the life expectancy in untreated cancer of the larynx is one year in 50 per cent of patients and that 95 per cent die within two years.

In no other internal organ of the body does cancer cause symptoms so early as it does when it occurs within the larynx. In the great majority of cases, laryngeal cancer begins as a lesion of the vocal cord. Here even a minute growth interferes with the normal function of the cord, and this interference is expressed as an alteration in the voice, progressing with time to a persistent hoarseness. Such hoarseness is so suggestive of something more serious than a simple laryngitis that the axiom, "In persistent hoarseness of two weeks' duration think of cancer, tuberculosis and syphilis," should never be forgotten.

Just as no other internal organ of the body produces a symptom so early as does cancer of the larynx, no other internal organ of the body can be so easily examined. In spite of these facts, it is not unusual to see not only patients with a history of hoarseness of months' and even years' duration who have received no medical advice, but also, and in too many cases, those who have been treated by gargles or sprays without the benefit of a laryngeal examination. Yet an examination of the larynx does not require unusual skill. A reflected light and a laryngeal mirror comprise the necessary equipment — and a few minutes of time.

In early laryngeal cancer the examination often reveals a proliferating new growth of the vocal cord and, in the vast majority of cases, it is the anterior half of the cord that is involved. Such a lesion is relatively benign; the lymphatics are few and scattered, so that the growth may persist for months and still be local. As the cancer slowly infiltrates along the long axis of the cord, it finally reaches the posterior half of the cord, where the lymphatics are more numerous, and from then on its progress is rapid. Fixation of the cord signifies that the cancer has infiltrated through the mucous membrane into the muscle of the cord or into the cricoarytenoidal joint. It is no longer a lesion of the mucous membrane. From the posterior portion of the cord the cancer spreads to the subglottic space, into the ventricle, into the false cord, to the arytenoid and aryepiglottic fold, and frequently to the esophagus and to the cervical lymph nodes.

Laryngeal cancer that is untreated or that fails to respond to treatment terminates with extreme suffering and a lingering death. Laryngeal obstruction means a fight for air, relieved only by tracheotomy. Extension to the mouth of the esophagus blocks the lumen so that the patient drools, since he cannot swallow his own saliva. Gastrostomy for feeding is frequently necessary. Involvement of the superior laryngeal nerve means severe pain, frequently referred to the temporomandibular joint or to the ear.

Just as no other internal organ of the body produces so early a symptom as does the larynx in cancer, and just as no other internal organ is so easily examined, so in no other internal organ of the body does cancer present a larger series of cures than it does in the larynx.

The limits of time do not permit a detailed discussion of the treatment of laryngeal cancer. The selection of the treatment is a highly individual one, and no hard and fast rule can cover every case. The location of the growth, the extent of the lesion, the degree of malignancy and the degree of cord fixation, as well as the physical condition of the patient, should determine the plan of treatment.

The ideal treatment is one that not only eradicates the disease but also leaves a normal physiologic state. External irradiation answers these requirements. Laryngeal cancer that responds to irradiation leaves the patient with a normal, or nearly normal, useful voice.

Cancer of the larynx may be classified as follows: Group I — small localized lesions of the vocal cord; Group II — extensive cordal or subglottic intrinsic growths; and Group III — intrinsic involvement with extrinsic extension.

In Group I, the small localized cordal growths, irradiation is to be preferred if the cancer is of Grade III or IV according to Broder's classification, and surgery if it is of Grade I or II. Surgery has in its favor that it can be performed under

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1943.

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local anesthesia; that the operative mortality is less than 1 per cent; that the period of hospitalization averages ten days to two weeks; and that unless the vocal process is removed there is frequently a regeneration of the vocal cord. When the case has been properly selected as suitable for laryngeal surgery by laryngofissure, a three-year to five-year cure can be obtained in approximately 75 to 82 per cent of cases, depending on the knowledge and skill of the operator.

In Group II, where there is cord involvement with subglottic extension, most radiologists agree that the carcinoma is not radiosensitive and that irradiation should not be used. Surgery offers only a total laryngectomy as a hope of cure.

In Group III, the extensive intrinsic and extrinsic carcinomas, particularly those of Grade III or IV, irradiation is the treatment of choice, although it may be only palliative.

The history of total laryngectomy is interesting. It is a little more than fifty years since Dr. J. Solis-Cohen,[1] assisted by Dr. W. W. Keen, operated on Daniel Hickey, performing the first successful total laryngectomy in the United States. Improvement in anesthesia as well as in surgical technic has robbed this operation of its high mortality. Among 53 patients, I have lost 2 from conditions attributable to the operation. One died from pneumonia on the sixth postoperative day, and the second from cardiac failure on the eighteenth postoperative day, on the eve of her discharge from the hospital.

From the earliest writings concerning cancer of the larynx to the most recent ones, total laryngectomy has often been described as a mutilating procedure leaving its victim in a pitiable condition — one that is worse than death. The psychic reaction to the loss of the power of speech, it is said, frequently leads to suicide or to insanity.

The medical profession and the public are familiar with the blind, the deaf and the crippled. Neither the public nor the vast majority of physicians are familiar with the patient who has lost his larynx and consequently the power of normal speech. It is a human failing to avoid the unknown. There is need of educating the medical profession as well as the laity to an understanding that the laryngectomized patient is not a pitiable creature who has given up all that life holds dear. It is hard properly to evaluate human suffering. The blind say that they would rather be blind than deaf; the deaf, that they would rather be deaf than blind; but the patient without a voice considers himself fortunate that he is neither blind nor deaf.

In advising the total removal of the larynx, one must appreciate the readjustments the patient must make and must evaluate his ability to make them. His mental outlook should be given serious consideration. The patient who lives wholly within himself — the self-centered, brooding person who faces any crisis with the greatest difficulty — is poor material to make the mental readjustment necessary after total laryngectomy.

Although the larynx is described as the organ of speech, it is not necessary for speech. Useful audible speech may be obtained after removal of the larynx by use of the so-called "artificial larynx," as developed by the laboratories of the Bell Telephone Company, or by re-education and development of the so-called "esophageal voice."

The artificial larynx consists essentially of a flexible, noncorrosive metal reed that is placed in juxtaposition to a rubber membrane inside a brass sound box, a mouthpiece that fits into a metal stem at the top of the sound box and a flexible connection to the tracheal stoma. When this apparatus is being used for speaking, the air is inhaled through the hole in the side of the sound box and passes through the metal tube in its bottom, down through the rubber connecting tube and through the tracheal connection into the lungs. The air when exhaled tends to pass out by the way it entered, but if the hole in the side of the sound box is closed by the finger or thumb, the air is forced out around the reed. This causes the reed to vibrate and to produce sound, which passes out through the stem in the top of the sound box and to the rubber mouthpiece into the mouth, to be converted into speech. The artificial larynx is supplied to the patient early after the operation so as to offer a positive substitution for the lost power of speech.

The esophageal voice depends on the esophagus' acting as an air chamber. The patient inflates his esophagus by swallowing air, creating a positive pressure that is thrown into air currents at the side of the tongue when its base is closed against the posterior pharyngeal wall. With exercise and training this action becomes automatic. (Dr. Schall then demonstrated 2 cases as examples of the successful use of these devices. In one, the patient had received a total laryngectomy, and by means of an artificial larynx was able to carry on successfully his work as a plumber. In the other, the patient was treated by external irradiation for an extensive carcinoma of both vocal cords. For three years he was free from disease. With recurrence and with the skin unable to stand further radiation, a total laryngectomy was performed. The patient developed an esophageal voice that permits him to continue his work as a fireman.)

Conclusions

In carcinoma of the larynx, as with cancer elsewhere, early diagnosis is of prime importance.

External irradiation is the ideal treatment, and it leaves a useful voice.

Laryngofissure, when indicated, gives a 75 to 82 per cent five-year cure.

Total laryngectomy, when necessary, does not always wreck the life of the patient, for this result can be avoided by the use of an artificial larynx or of an esophageal voice.

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REFERENCE

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ERYTHROBLASTOSIS FOETALIS*

Report of a Case

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EVER since Diamond, Blackfan and Baty[1] in 1932 first designated as erythroblastosis foetalis a syndrome characterized by the triad of hydrops, icterus gravis and anemia of the newborn, this interesting disease has been studied intensely. Darrow[2] in 1938 first suggested isoimmunization by the mother against fetal red cells as the basic etiology, but had no means of proving this theory. Levine and Stetson[3] in 1939 were the first to point out that isoimmunization of the mother through the fetus can occur. Landsteiner and Wiener[4] in 1940 discovered the occurrence of the Rh factor in 86 per cent of human beings as a dominant mendelian gene, and Levine with his co-workers[5, 6] since 1941 have accumulated many data to prove that the Rh factor is at least one of the major etiologic causes of erythroblastosis foetalis. Javert[7, 8] accepted the Rh factor as one of the causes, but suggested other necessary factors as further underlying conditions.

Most of the evidence, however, points to serologic phenomena, and erythroblastosis foetalis is most probably the outcome of an isoimmunization resulting from fetal antigens and subsequent hemolysis of the fetal red cells by maternal antibodies produced by these antigens, and transmitted from one circulation to the other in a process of diapedesis and dialysis.

Recently, a case of erythroblastosis foetalis of atypical form was observed in an infant who displayed icterus gravis as well as neonatal anemia, but no hydrops congenitum. A prompt diagnosis led to transfusions and resulted in cure and survival.

CASE REPORT

C. W., a 14-day-old boy, was admitted on October 14, 1942, with known intense jaundice of 5 days' duration. He was the second child of young, healthy parents, and was born at home without instrumentation. At birth he appeared normal and the attending obstetrician observed no untoward symptoms or signs. The birth weight was not recorded, but the child appeared well developed. On the 9th postnatal day, a deep icterus became apparent and reached its maximal intensity 24 hours later. On admission the weight was 7 pounds, 2 ounces.

Both parents gave negative Wassermann and Kahn reactions. The mother was 19 years old and had a daughter of 21 months, born at term, who had at no time shown any degree of jaundice. She denied any miscarriages or stillbirths. The father was 24 years old and was jaundiced in infancy. Otherwise the family history was negative.

Physical examination was negative except for an intense icterus of the entire body. Enlargement of abdominal organs, and especially of the spleen and liver, could not be demonstrated by several examiners nor by a consultant, and roentgenograms of the long bones taken on October 16 gave no evidence of any pathologic lesions. The fragility test was negative, since hemolysis occurred in sodium chloride solutions ranging from 0.44 to 0.32 per cent, whereas in a normal control it occurred in solutions ranging from 0.40 to 0.30 per cent. A tentative diagnosis of erythroblastosis foetalis was made, substantiated by subsequent consultation and serologic studies by Dr. Philip Levine, of Newark, New Jersey. A total of three transfusions was given at intervals of about once a week. The essential features of the hemograms will be discussed in detail.

Serologically the father was Type A and the mother was Type O. The patient was also Type O, as was a sister of the mother. Agglutination of the patient's red cells by the mother's serum was positive, although both were Type O. This indicated the presence of some substances in the mother's serum that agglutinated the red cells of the infant. These substances were later proved to be anti-Rh agglutinins.

The initial hemogram of the patient gave a count of 1,520,000 erythrocytes. The white-cell count was 42,000, with 39 per cent mature and 6 per cent immature polymorphonuclear leukocytes and 5 per cent myelocytes, as well as 4 per cent nucleated red cells. The hemoglobin was 32 per cent (Sahli), and the color index 1.06. Marked anisocytosis and polychromasia were present in this as well as in all subsequent stained smears except the last. During the next 2 days the red-cell count fell to 1,500,000, and the white-cell count to 34,000, with 30 per cent polymorphonuclear leukocytes and 18 per cent myelocytes; the nucleated erythrocytes increased to 7 per cent.

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On October 17, a transfusion of 50 cc. of whole blood from a professional donor of Type O was given without regard to the Rh factor. The red-cell count reached a maximum of 2,290,000; the white-cell count decreased to 12,300, with a minimum of 19 per cent polymorphonuclear leukocytes, and an additional 8 per cent immature and 8 per cent myelocytic granulocytes. The hemoglobin rose to 46 per cent, with a color index of 1.04. Simultaneously with the first transfusion, 1 mg. of vitamin K and 0.3 cc. of liver extract were given daily, and the patient showed a normal weight-increase curve.

On October 23 the red-cell count had fallen to 2,090,000. The white-cell count was 18,500, with 24 per cent mature and 5 per cent immature polymorphonuclear leukocytes and 9 per cent myelocytic granulocytes, and 6 per cent nucleated red cells. The hemoglobin was 39 per cent, with a color index of 0.89. A second transfusion of 50 cc. of whole blood was therefore given from the original donor, after routine cross matching at room temperature. This transfusion was followed by fever and facial twitchings of the recipient. The red-cell count reached 3,000,000 the day after the transfusion. The white-cell count fell to 11,600 after a slight increase during the period of reaction. The polymorphonuclear leukocytes increased to 33 per cent, the immature granulocytes remained stable at 5 per cent, and the myelocytes decreased to 5 per cent. The nucleated erythrocytes reached a maximum, 16 per cent, on the day following the transfusion, decreasing to zero 5 days later. The hemoglobin increased to 62 per cent, whereas the color index remained stable at 1.03. Physical examination revealed that the icterus had greatly decreased and that the weight had increased in a regular curve.

On November 2, a third transfusion of 50 cc. of whole blood was deemed necessary to hasten complete recovery. A new donor was found in the mother's sister, whose cells were compatible by Levine's[9] modified cross-matching technic.* Following this transfusion the red-cell count rose rapidly to 3,000,000, at which level it stabilized, with complete disappearance of the nucleated erythrocytes. The white-cell count rose from 13,900 to 28,000 owing to a minor skin infection, but decreased in a few days to 17,000. The polymorphonuclear leukocytes increased steadily from 30 to 55 per cent, the immature as well as the myelocytic granulocytes disappeared, and the hemoglobin reached 60 per cent, with an average color index of 1.0. The icterus disappeared completely, and by November 21, when the patient was discharged, the weight had reached 8 pounds, 8 ounces. The anisocytosis and polychromasia had disappeared.

Blood samples of the mother were submitted to Dr. Levine, who gave the following report:

> The mother's blood is in Group O; it is Rh-negative with each of the three varieties of anti-Rh serums, and positive with anti-Hr serum. The serum contains anti-Rh agglutinins with a titer of about 1:50 and its specificity corresponds to that of an anti-Rh_1; that is, it gives 85 per cent reactions.

Subsequent physical examination and hemograms of the patient were negative. He was last seen on January 26, 1943, or 2 months after discharge, at the age of 4 months. He appeared physically well and displayed no signs of jaundice or other residual, and was considered cured. The red-cell count was 4,290,000 and the white-cell count was 13,000, with 34 per cent polymorphonuclear leukocytes plus 2 per cent immature granulocytes. The hemoglobin had risen to 78 per cent, with a color index of 0.90. Neither anisocytosis nor polychromasia was evident. It should be pointed out that the severe icterus and the facial twitchings during the course of the disease may very well have been associated with kernicterus, and that, therefore, cerebral palsies and retardation in physical and intellectual development must be watched for during the next 6 months to be certain that this damage did not occur.

*The tubes are incubated at 37°C. for thirty minutes, then centrifuged at 500 r.p.m. for one minute; they are then inspected for agglutination, both grossly and under the microscope.

Discussion

The importance and role of the Rh factor in the pathogenesis of erythroblastosis foetalis and its logical therapy were well pointed out by Levine and his co-workers[5, 6] in 1941–1942. The existence of qualitative differences in the Rh agglutinogens in human Rh+ blood was first demonstrated by Wiener[10] in 1941. Levine[9] in 1941 claimed that about 90 per cent of intragroup transfusion reactions are due to isoimmunization, either because of repeated transfusions or because of diapedesis of fetal blood in Rh– women, although anti-Rh agglutinins cannot always be demonstrated. He assumed that the anti-Rh antibody is fixed to the tissue cells of the reticuloendothelial system. To prevent such accidents all Rh– recipients should be transfused with Rh– blood only. In cross matching, the patient's serum and donor's cells should be incubated at 37°C. for the fifteen to thirty minutes before the result is reported, since anti-Rh agglutinins frequently behave like warm agglutinins, as in the present case. However, even this modified cross-matching technic is reliable in less than half of the cases, and should not take the place of typing for the Rh factor in well-organized hospitals and medical centers. Levine's[9] article should be consulted for details of the modified cross-matching technic.

The clinical triad of erythroblastosis foetalis consists of fetal hydrops, icterus gravis neonatorum and neonatal anemia. This patient presented a deep icterus as well as neonatal anemia with excessive normoblasts and progressive decrease of the peripheral red-cell count. However, the fact that hemolysis became grossly evident as late as nine days after birth does not argue against the isoimmunization theory of erythroblastosis foetalis, since several authors have made such reports. The suggestion has been advanced that the delayed reaction — that is, hemolysis — may be produced in breast-fed infants by the ingestion of colostrum. This, however, does not pertain to our observation, since the patient was bottle fed. Another theory holds that the agglutinins of the mother can be stored in the fetal tissues or remain in combination with other red cells, to be released

later, although it is not as yet clear what mechanism brings about this release. Yet this last theory may be applied to the present case, in which after transfusion with nonagglutinating blood jaundice apparently became clearly visible nine days after delivery, and in which isoagglutinins were demonstrated in the mother's blood. Furthermore, (third transfusion) higher hemoglobin levels and red-cell counts were maintained.

The theory of Levine and his co-workers is in essence that 87 per cent of all human beings are Rh+ and 13 per cent are Rh–. Levine et al.[5, 6] also found that 90 per cent of mothers whose infants developed erythroblastosis foetalis were Rh–, and all these women were married to Rh+ husbands. If an Rh– woman bears a child by an Rh+ man, all offspring will be Rh+ if the husband is homozygous, but only half if he is heterozygous (mendelian dominant), and only these may develop erythroblastosis. This occurs oftener in the second Rh+ child (as in our case) and in subsequent children, since isoimmunization is said to be initiated by the first pregnancy. During this period of isoimmunization the Rh+ red cells from the fetus apparently pass through the placental membranes into the Rh– maternal circulation, where they stimulate the production of antibodies. These antibodies then pass back into the fetal circulation, and if they there attain a suitable concentration produce agglutination and, secondarily, hemolysis of the fetal red corpuscles, the equivalent of the agglutination effect in vitro.

At birth the fetal and maternal circulations are permanently severed and the exchange of Rh+ cells between fetus and mother and of anti-Rh antibodies between mother and fetus ceases. Yet fetal hemolysis will continue until all anti-Rh antibodies are neutralized — that is, used up. This occurs normally in eight to fourteen days post natum unless the hemolysis is so severe as to bring about fetal death. At autopsy, even the brain nuclei may show deep jaundice (kernicterus), a characteristic peculiar to 25 per cent of cases in which death is due to erythroblastosis foetalis. To combat this hemolysis in the infant, frequent transfusions of Rh– cells are required, since these cells cannot be hemolyzed by the anti-Rh antibodies, and thus sufficient erythrocytes are left to maintain vital functions. The infant will, however, counteract this hemolysis also by increased red-cell production. The result of this increased hemopoiesis is the appearance of many nucleated erythrocytes in the peripheral blood stream, another characteristic of this neonatal anemia.

Javert[8] gave the incidence of erythroblastosis foetalis of all types as 0.23 per cent, and its cause of fetal death as 3.2 per cent. The nearer to term the disease develops the better is the prognosis. It occurs more frequently in multiparas than in primiparas since preceding pregnancies predispose to it. Javert concurs to a large extent with the theory of Levine, but finds sufficient exceptions to maintain that the Rh factor cannot be the sole cause of erythroblastosis foetalis, since other agglutinogens may also produce isoimmunization of the mother.

Summary and Conclusions

A case of erythroblastosis foetalis with icterus gravis and neonatal anemia in a nine-day-old infant is reported, and the recent pertinent literature and theories are briefly reviewed.

Serologic studies substantiated the fact that the Rh factor was at least one of the major etiologic causes in the pathogenesis. However, it seems that other fetal antigens may also stimulate the production of maternal antibodies that bring about fetal hemolysis as late as nine days post partum. The true mechanism of development is still obscure, but it seems that the antibodies can be stored, or may at least remain latent, in the fetal red blood cells or tissues even after separation of the two circulations, and can be liberated by still unknown processes. Ingestion of colostrum did not produce their liberation in the present case.

Therapeutically, repeated tranfusions of properly selected and cross-matched blood, preferably by anti-Rh serum, or by Levine's modified technic, are the only successful methods. It should be stressed that Rh– blood is important for the infant with erythroblastosis foetalis for at least the first week after birth. This need becomes less and less important as evidence of hemolysis diminishes in the second and third weeks of life.

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HISTAMINE BY MOUTH IN THE TREATMENT OF VASOMOTOR RHINITIS*

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SINCE the work of Dale and Laidlaw[1] on the role of histamine in anaphylaxis and allergy was published in 1919, many papers on this subject have been written. Ramirez and St. George[2] first attempted the use of histamine as a therapeutic agent, but with inconclusive results. Stahl and Masson[3] applied histamine to skin scarifications and had encouraging success, although the technic of dosage was crude. Dzsinich[4] emphasized the importance of extremely small doses and worked out an effective scheme of treatment. Alexander and Elliott[5] had excellent results in urticaria with intravenous injections of large doses. Attention should also be paid to the papers by Farmer,[6-8] who reports a great number of cases treated with Dzsinich's technic and gives a complete review of the work done in this field.

Although most of the investigators have tried to imitate the technic used in specific desensitization, and to build up a so-called "specific nonspecific" resistance to histamine by giving frequent and steadily increasing doses, a few — mostly accidental — observations have shown that histamine has an immediate beneficial effect in the allergic manifestation. Thus far only Stahl and Masson have tried to use this effect in therapy. They applied histamine by skin scarifications during an attack of asthma and observed a beneficial effect.

Since the effect of histamine is almost immediate and is transient, it is evident that the drug should be given at frequent intervals. For the average patient, injection, whether given by the intradermal, subcutaneous or intravenous route, is impractical, and we have been led to investigate further the effectiveness of giving histamine by mouth.

Although it is generally considered that histamine is largely destroyed by the gastric juices, there are a few reports in the earlier literature indicating that small amounts may be absorbed through the intestinal wall (Meakins and Harington,[9] Ivy and McIlvain[10] and Koessler and Hanke[11]).

That histamine given by mouth is absorbed promptly and has a definite action is shown by the variety of toxic effects. For example, one of our patients developed a characteristic flushing of the face within ten minutes after taking 13 drops of a 1:1000 dilution of histamine, and all treatment with histamine had to be discontinued because of severe menstrual pain. In another case, severe headaches occurred regularly within ten minutes after each dose of histamine, but they subsided in another ten minutes. Three patients developed abdominal cramps and pain following the taking of histamine. One of them had taken the drops shortly after a highball, and it is likely that the permeability of the stomach wall was altered by the alcohol. One of us (R. J. S.) has had abdominal cramps repeatedly following experimental doses of histamine.

Even more suggestive are specific reactions in which the original symptoms are duplicated. Thus, when histamine is given in doses larger than the empirically established optimum, patients with vasomotor rhinitis may have increased nasal obstruction or rhinorrhea, and those with asthma develop a wheeze.

It is apparent that histamine is absorbed from the gastrointestinal tract and that the same physiologic reactions are obtained as with parenteral injection.

The technic for its administration by mouth requires close attention to details. The therapeutically effective dose varies greatly among patients, but for each it remains quite constant over a long period of time. Our method is to start with a 1:1000 dilution and a dose of 1 drop in a glass of water. The patient is asked to observe the reaction closely. He finds that too large a dose aggravates his symptoms and too small a dose causes no change, but that the correct dose relieves him within fifteen or twenty minutes. If there are no bad effects, he is advised to increase the dose by adding 1 drop each day until toxic effects appear. Thereafter he is maintained on the dose that is just below the toxic level, and this dose is repeated as often as is necessary to control the symptoms.

The dose may vary from 1 drop of a 1:1000 dilution to 25 drops of a 1:100 dilution, but the average dose is 5 to 7 drops of the 1:1000 dilution. The necessity for perseverance and for intelligent cooperation by the patient is obvious. In most of our patients, oral histamine therapy was given only

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TABLE 1.

Case No.	Hospital No.	Sex	Age	Age at Onset	Familial History of Allergy	Positive Skin Tests
			yr.	yr.		
1*	374067	M	23		+	Pollen
2	371450	M	12		-	None
3	209434	F	39	34		Pollen, dust wheat and feathers
4	354350	M	64	22	-	Wheat
5	121308	F	49	44		Animal hair, dust, kapok, orris, wheat and Alternaria
6	148644	F	22	10		Pollen
7	367109	F	22	15	-	None
8	369445	F	40	39	-	None
9	24672	F	21	16		Feathers
10	325777	F	23	22	-	Kapok, orris, dog hair, dust and ragweed
11	313471	M	54	54	-	Feathers
12	372486	F	18	16		None
13	264193	F	42	25	-	Kapok, orris, pyrethrum and cat hair
14*	203782	F	41	41	+	Ragweed
15	377093	F	27	19	+	None
16	187845	F	28	26	-	None
17	369560	F	45	35	-	Many, including pollen
18	160532	M	48	44		None
19	366737	F	14	14	-	None
20	331470	F	42	34		Ragweed, kapok, goose feathers, orris, Alternaria, dust and cat hair
21	10257	F	41	34		None
22	357832	F	21	21		None
23	298733	F	42	40	+	Orris, house dust and pyrethrum
24	41826	M	12	11	+	None
25	366441	F	24	19	+	None
26	171475	M	58	45	+	None
27	356021	F	31	31	-	None
28	107864	F	79	74	+	None
29	306894	F	35	23	-	Cherry
30	307068	F	15	14		House dust, kapok and wheat
31	378117	F	35	35		Ragweed, house dust, feathers, egg white and dog hair
32	178422	F	35	32	-	Orris and wheat
33	102205	F	32	27	-	Feathers

Case No.	Previous Treatment: Kind	Previous Treatment: Result	Optimum Dosage of Histamine	Result	Remarks
			drops		
1	None		7 (1:1000)	None	Patient unco-operative
2	None		1-5 (1:1000)	Excellent	Effect immediate
3	Vaccines	None	12 (1:1000)	Excellent	
4	Wheat injections	None	15 (1:1000)	Complete relief	
5	Vaccines and elimination	Slight improvement	6 (1:1000)	Excellent	
6	Pollen injections	Slight improvement	23 (1:1000)	None	Patient unco-operative
7	Vaccines	None	5-7 (1:1000)	Good	
8	None		1-2 (1:1000)	Good	
9	Vaccines	None	5-6 (1:1000)	Excellent	Abdominal cramps
10	Vaccines and elimination	None	2 (1:1000)	Fair	
11	Vaccines and elimination	None	10 (1:1000)	Excellent	
12	None		1 (1:1000)	Excellent	
13	Vaccine and nasal therapy	None	5-15 (1:1000)	Fair	Effect diminished in spite of larger doses
14	None		2-3 (1:1000)	Excellent	
15	Ephedrine packs	None	3-4 (1:1000)	Complete relief	Nasal mucosa became normal
16	Vaccines and elimination of dust	None	7 (1:200)	Good	Results affected by menstruation
17	Ragweed injections	None	4 (1:1000)	Complete relief	
18	Vaccines and nasal therapy	Moderate improvement	8-13 (1:1000)	Slight or none	Patient unco-operative
19	None		15 (1:1000)	Excellent	
20	Vaccines and elimination	None	7 (1:1000)	Excellent	
21	Vaccines and nasal therapy	None	12 (1:1000)	Good	
22	None		6 (1:1000)	Excellent	
23	Dust injections and nasal therapy	None	3 (1:1000)	Excellent	Abdominal pain
24	Vaccines	None	15 (1:100)	None	Symptom free at seashore
25	None		3-4 (1:1000)	Excellent	
26	Vaccines	None	6-12 (1:100)	Good	
27	Vaccines	None	6 (1:1000)	Excellent	
28	Vaccines	None	2 (1:1000)	Excellent	
29	Dust injections and elimination	Slight improvement	5-15 (1:1000)	Fair	Large doses required during menstruation
30	Vaccines and elimination	Slight improvement	11 (1:1000)	Excellent	
31	Elimination	None	17 (1:200)	Excellent	
32	Vaccines and orris injections	Slight improvement	11 (1:200)	Excellent	Beneficial effect eventually lost
33	None		16 (1:100)	None	

*Case of hay fever; all others, vasomotor rhinitis.

after treatment with other methods had been followed, often for years, without success.

Two of us (J. C. G. and R. J. S.) have made routine use of histamine in treating a large group of private patients suffering from vasomotor rhinitis during the last four years. We are convinced of its value as an agent for symptomatic relief. Unfortunately, however, the private cases cannot be included in a statistical report because other therapeutic procedures—vaccines, thyroid and diets—were used at the same time with the histamine.

To test the value of histamine alone, a small group of clinic patients was selected, and, as a rule, no changes in their routine way of life were made except to prescribe histamine in doses as described above. Forty cases of perennial vasomotor rhinitis and 6 of seasonal hay fever were chosen. Of this group 13 were lost and the end results are unknown. The balance (33 cases) are listed in Table 1. In 3 cases, treatment had to be discontinued because of the lack of co-operation by the patient. Of the remaining 30 cases, 1 (Case 24) showed no effect up to a dose of 15 drops of 1:100 dilution, and in another (Case 33) there was temporary relief from 5 drops of 1:1000 dilution, but the patient later became refractory and doses up to 16 drops of 1:100 dilution were ineffective. In the other 28 cases, histamine produced repeatedly or regularly an immediate beneficial effect on the nasal symptoms, and most of these patients have been followed over a period of several months. This series is being rapidly extended, and histamine is being tried in other conditions with results that will be reported later.

The most striking therapeutic effects so far observed have been seen in the cases of vasomotor rhinitis. In such cases, within ten to twenty minutes after a dose of histamine by mouth the symptoms cleared and nasal obstruction, sneezing and watery discharge ceased. The benefit is more marked than that derived from ordinary nasal sprays or drops, and it usually lasts for several hours. In rare cases the symptoms return in less than an hour, but in others the relief from a single dose lasts for a full day or more. When the symptoms recur, another dose is taken, with the same effects. This immediate symptomatic relief is the main objective of our technic, and it should be noted that the effect of single doses is prolonged as time goes on—that is, histamine is needed less and less frequently. Patients who in the beginning needed six or eight doses of histamine daily, after a few weeks of treatment needed only two or three doses daily, and later on only occasional doses once every few days.

The following case reports illustrate the method and the results:

Case Reports

Case 17. This 45-year-old, married woman had had a stuffy nose persistently since the age of 35. She had also had migraine. Skin tests were positive for a large number of allergens, among them ragweed. Ragweed injections were given weekly or biweekly from July 31 to September 8, 1942, without improvement. During October, the patient's condition became somewhat better, but nasal obstruction persisted. On October 19, histamine treatment was started. On November 9, the patient reported on her 3 weeks' experience: doses up to 3 drops of 1:1000 dilution had been ineffective, but 4 drops brought complete relief within 20 minutes. In November, she was taking 4 drops once a day before bedtime and was sleeping the whole night.

Case 25. This 24-year-old, married woman had had perennial vasomotor rhinitis and headaches since the age of 19. She had had attacks of urticaria for years, and had suffered from cold hands and feet as long as she could remember. Her father had had hay fever. Her nose had been packed with ephedrine but without any permanent effect. On September 28, 1942, the nasal mucous membranes were pale and boggy. Skin tests were negative. Therapy with histamine in 1:1000 dilution by mouth was begun on October 5. On October 13, 3 to 4 drops of this dilution relieved the headaches and the nasal obstruction within 15 to 20 minutes. On November 2, the headaches and nasal obstruction had developed only once during the last 3 weeks and were promptly relieved by 4 drops of histamine. On November 6, examination of the nose showed normal mucous membranes. Meantime, however, the urticaria remained unimproved and the patient had daily eruptions. A new oral course of histamine was started.

Case 9. This 21-year-old woman had had perennial vasomotor rhinitis since the age of 16. Intradermal tests had been positive for goose feathers, but elimination of feathers and dust as well as treatment with vaccines had been of no benefit. On August 4, 1942, oral doses of histamine in 1:1000 dilution and of thyroxin were begun. On August 18, the patient was still sneezing but 6 drops of histamine always brought relief. The dose caused stomach cramps, however, and the treatment had to be discontinued. Through the fall histamine was tried off and on, but always with the same effect. A dose of 6 drops brought relief from nasal symptoms, but they caused stomach cramps. When the drops were taken before meals instead of after them, 4 drops was ineffective, but 5 drops gave complete relief and the stomach pain was much less severe.

Case 4. This 64-year-old baker had had chronic vasomotor rhinitis since the age of 22, becoming worse recently. Nasal discharge and sneezing made it difficult for him to work. During a vacation in Florida in the winter of 1941–1942 he was entirely free from symptoms, but on the first day of work on his return, sneezing and nasal discharge began again in full strength. From May 25 to October 2, 1942, injections of wheat extract were given each week, but with hardly any improvement. On October 2, a vaccine injection was given and oral histamine therapy, combined with thyroxin in doses of 30 mg. twice a day, was begun. On October 23, doses of histamine up to 14 drops of 1:1000 dilution had been ineffective, but 15 drops gave regularly almost complete relief. If this dose was taken every morning before going

to work the nose cleared within 15 to 20 minutes and remained clear during the time at work. Only this single dose was needed each day. On November 20, the patient was still well.

Case 28. This 79-year-old, married woman had had a stuffy nose since the age of 74. Treatment with vaccines had been of no benefit. On October 1, 1942, she was miserable with continuous nasal discharge and sneezing and was unable to sleep. Histamine by mouth was begun. On October 22, she took up to 6 drops of 1:1000 dilution. Relief came from 1 or 2 drops, but she misunderstood the directions and increased the quantities. As a result, her nose ran more than ever. As soon as the dose was reduced to 2 drops, however, relief was obtained. On November 23, the patient was taking this small dose four or five times a day and felt better than she had for 4 years.

Summary and Conclusions

The occurrence of good results in all except 2 of 30 cases is more than a coincidence. That histamine is absorbed from the gastrointestinal tract is demonstrated by Farmer's results in guinea pigs and by the occurrence of toxic reaction as reported above. The object has not been to build up a general resistance to histamine but rather to control the symptoms by repeated small doses. The wide variation in patients' susceptibility to histamine is very interesting and constitutes the chief difficulty, if not the actual danger, in treatment of this sort. In the present series, once the proper dose was determined, other doses of this same size repeated their physiologic effect from time to time indefinitely. It has also been observed that the good effect of single doses seems to last longer as the treatment is continued for weeks or months.

This observation somewhat contradicts the current attempts to explain the effect of histamine in allergic diseases on the basis of mithridatization of a desensitization against histamine.

Histamine is sometimes less effective during menstruation or a few days before it. This is understandable in view of the fact that allergic manifestations are frequently more severe at this time. The effectiveness of histamine and therefore the size of the dose depend also on the functional state of the stomach. The amount of histamine that passes undestroyed through the wall of an empty stomach is quite different from that which is absorbed at the height of gastric activity. Because the dosage of histamine is so delicate and the variations in absorption so great, it is imperative to maintain basic conditions rigorously. It seems advisable to take histamine only before meals, when the stomach is empty.

Sometimes unpleasant by-effects cannot be avoided. If severe stomach cramps appear at the level that gives therapeutic results, or if menstruation is strongly affected, it may become necessary to discontinue the treatment as was the case in 3 of this series.

Oral histamine therapy is not a panacea. Much work remains to be done on the problem, but so far it can at least be said that it brings results that are definitely superior to those obtained by the other methods of treatment of vasomotor rhinitis, which are so cumbersome and unsatisfactory.

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MEDICAL PROGRESS

THE DIAGNOSIS OF GOUT*

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THE diagnosis of gout is frequently not made because the patient does not exhibit the classic features of chronic gout. This common diagnostic error and the ensuing therapeutic mistakes will continue to occur unless physicians become increasingly alert to the various manifestations of the disease. It is hoped that this treatise, dealing solely with those features pertaining to diagnosis, will help serve the above purpose.

Gout is a hereditary constitutional disease, preeminently of males, occurring at any age and in most cases characterized by recurring attacks of acute arthritis. The clinical picture may, however, vary from an asymptomatic hyperuricemia to a severe, crippling joint disease even in the same patient. The articular inflammation of both acute and chronic gouty arthritis is caused by deposits of sodium urate (tophi), which may also be found in many other tissues. Although the exact etiology of the disease remains unknown, it is rightly classed as one of inborn metabolism, the fundamental metabolic defect, the inability of the organism to dispose of uric acid, being evidenced by a hyperuricemia. The latter may be present long before the ailment assumes its striking articular form. Space does not permit a discussion of the various theories advanced to explain the altered excretion of urates, the hyperuricemia and the formation of urate deposits in the tissues. It is sufficient to state that these phenomena remain three of the enigmas of the disease.

PATHOLOGY

Only those pathological features of the disease that pertain to a better diagnostic understanding will be discussed. The changes observed are dependent on the deposition of sodium urate in the various tissues and the inflammatory and degenerative changes resulting therefrom. The urate deposits surrounded by tissue exhibiting inflammatory and foreign-body reactions constitute the one pathognomonic lesion of the disease, and are readily demonstrated provided the tissues to be examined are properly fixed and stained.[1] Many of the anatomic alterations observed in the late stages of gout are the result of the ill-understood arterial and arteriolar sclerosis that frequently manifests itself as the disease advances.

Deposits of urate in articular structures are the cause of the most frequent disability resulting from gout. No joint is exempt, although certain ones are more frequently involved than others,[2-4] for example, the joints of the lower extremities as compared to those of the arms. The metatarsophalangeal joints of the great toes are most regularly affected and may be the only site. The small joints affected in order of frequency are those of the feet, the ankles and the wrists. The knees, elbows, shoulders and hips are less commonly involved. The sacroiliac and sternoclavicular joints and the articulations of the spine, jaw and larynx most rarely contain foci of urate deposition.

The term "tophus" has through general usage come to denote a urate deposit in tissues other than joints. These abarticular tophi are most commonly seen in the helix or antihelix of the ear, the olecranon and prepatellar bursae and the tendons of the fingers and wrists, toes, ankles and heels. Less frequently they are met with in the skin of the palms and soles, the tarsal plates of the eyes, the nasal cartilages, the fingertips, the tendinous expansion of the muscles and the cornea and sclerotic coat of the eye.[5] The kidneys may also be the seat of urate precipitates. Very rarely they have been found in the corpus cavernosum, the prepuce of the penis, the aorta, the myocardium and aortic valves, the tongue,[6] epiglottis and vocal cords, and the arytenoid cartilages. Occasionally the crystals have been recovered from the sputum of gouty subjects.[7] The isolated reports of urates in the central nervous system and its coverings have never been verified. Such abarticular deposits are followed by the foreign-body inflammatory reaction previously referred to, and vary in extent and degree with the vascularity of the affected tissue.

The renal lesions observed in gout have been called *gouty nephritis, gouty form of Bright's disease, interstitial* or *arteriosclerotic nephritis* and *renal impairment of gout.* This varied terminology indicates that no unanimity of opinion has

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*, Volume III. 678 pp. Springfield, Illinois: Charles C Thomas, 1942. $5.00).

*This is publication No. 73 of the Robert W. Lovett Memorial Fund for the Study of Crippling Disease, Harvard Medical School.

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The arthritis studies in this clinic were made possible by a grant from the Commonwealth Fund, New York City.

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existed concerning the nature of these changes, but all writers are agreed that the incidence of kidney disease is higher in gout than in other chronic disorders, such as rheumatoid arthritis, diabetes mellitus and pernicious anemia. Few if any, however, argue that anatomic alterations of the kidney can be demonstrated as the primary cause of gout.

The incidence of arteriosclerosis and hypertension is higher in gouty subjects than in a control group of comparable age.[8-11] The latter is usually a late manifestation. The triad of arteriosclerosis, nephrosclerosis and increased arterial tension frequently leads to hypertrophy of the left ventricle. Marked arteriosclerotic degeneration of the aorta is not uncommon. Extensive coronary and cerebral vascular disease may be the immediate cause of death. Other pathologic changes associated with the disease are similar in nature and extent to those found in any corresponding age group.

General Considerations

Incidence

The incidence of gout is unknown. Undoubtedly, many more cases are seen in private practice than in hospitals because acute gouty arthritis is, as a rule, self limited and of short duration. Hench[12] estimates that 5 per cent of all patients with joint disease seen at the Mayo Clinic have gout. This is a much higher incidence than has been found in most other clinics. The evidence derived from pathological studies reveals an incidence varying from 1 to 5 per cent.[13, 14] Despite such marked discrepancies, gout does not appear to be a rare or declining disease. As stated previously, the diagnosis frequently is not made because the patient fails to exhibit the classic features of chronic gout.

Heredity

The earliest medical writers have stressed the hereditary nature of gout. A familial incidence as high as 75 per cent has been observed.[2, 15, 16] The propensity of the disease to pass over one generation is a hindrance to the investigator gathering genealogic data. It is commonly stated that women, although infrequent victims of gout, are likely to transmit it to their children.[7] Thus, a patient may inherit his maternal grandfather's gout although his mother never experienced any clinical manifestations of the disease.

Sex

Slightly over 95 per cent of all patients affected with the disease are males. The explanation for this striking difference in the incidence of gout in the two sexes is unknown.

Age

Gout is an inherited disease. Its potentialities are assumed to be present at birth. The finding of hyperuricemia in apparently normal young relatives of gouty patients and its presence with or without tophi in adults for years prior to the onset of articular complaints indicate that the disease antedates the appearance of symptoms. It rarely manifests itself in infancy or adolescence. Acute arthritis occurs with increasing frequency in the second to the sixth decade, being commonest in the forties. The first evidence of the disease, however, may not appear until late in life. Cases are on record demonstrating the initiation of symptoms in the sixties, seventies and eighties. In such cases the attacks as well as the subsequent course tend to be mild. The converse is likewise true: onset at an early age frequently portends severe seizures, often polyarticular in distribution, and may lead to extensive crippling and severe vascular nephritis before middle life.

Race and Climate

There is at present no accurate information concerning the relevance to gout of either race or climate.

Habits and Occupation

Those who believe that gout is the nemesis of high living cite a higher incidence among people whose occupations are conducive to overindulgence in food and drink. Until more conclusive statistical information concerning the occupational incidence of the disease is available, it is impossible to evaluate past statements or to make further comment.

Clinical Manifestations and Course

The symptomatic or articular manifestations of gout are designated by various terms. The acute attacks, which are followed by complete remissions, have been called "acute gout" and "regular" or "acute recurrent gouty arthritis," in distinction from chronic gout, signifying chronic gouty arthritis with or without tophi. Because the disease runs an extremely diversified and irregular clinical course, the simple yet satisfactory classification of acute and chronic gouty arthritis has been generally adopted.

The onset of the first attack of acute gouty arthritis is as a rule dramatic. The patient, usually a healthy-appearing middle-aged man, is suddenly seized with severe, sometimes excruciating, pain, often in one of the metatarsophalangeal joints. Although such attacks frequently begin at night, they may occur at any time. Within a few hours of the onset, the afflicted joint becomes swollen, red, hot and exquisitely tender. The swelling may

appear so rapidly that within a few hours the patient is unable to remove his shoe without cutting it. The inflammatory edema is much more marked than in other acute arthritides and often extends some distance beyond the joint margins. Effusion into the large joints is not uncommon. At the peak of the attack the intense swelling of the foot, accompanied by redness and extreme heat, resembles septic inflammation or an extensive cellulitis. There may be an associated lymphangitis. The skin is red, tense and shiny. The superficial veins are distended. The pain, often described as crushing and usually worst at night, generally confines the patient to his bed or room because weight bearing is intolerable.

As tenderness and redness subside, pitting edema is demonstrable. With the disappearance of the swelling, the overlying skin become loose and thin and desquamation of the cutis and itching may follow. The combination of these findings is rarely encountered in other types of acute arthritis, and is therefore of singular diagnostic significance. The attack subsides spontaneously within ten days to a few weeks, with complete restoration of normal joint function.

Approximately 50 per cent of the initial attacks are confined to the first metatarsophalangeal joint, but not infrequently other joints are affected at the same time. The neighboring metatarsal and tarsal joints or those of the opposite foot may be involved simultaneously or in rapid succession. A bursa, more commonly over the olecranon or patella, may be the site of an attack. The younger the patient, the more likely is the attack to be polyarticular and migratory in nature. Fever, again more prominent in young patients, is usually mild, rarely lasts more than a few days, and may be absent. The severity of the initial attack varies greatly. In some cases the acute illness is extremely mild and lasts only a few days. Occasionally one sees abortive attacks.

Physical examination at the time of the initial attack of gouty arthritis is usually negative except for the articular findings. Maximal joint tenderness is usually present on the medial aspects of the involved joint. A tophus, unknown to the patient, may be found in the helix of the ear, indicating that the disease has been present for some time. The clinical course subsequent to the initial attack, although usually conforming to a distinct pattern, may vary considerably. Very rarely the patient remains symptom free altogether, or for an interval of many years, as exemplified by a case in which the initial seizure at twenty-seven years of age was succeeded by a second one sixty-two years later. In the benign form two to six distinct attacks may be scattered over a period of thirty to fifty years or concentrated in one of the middle decades of life.

The recurrent attacks of acute arthritis are commonly followed by remissions during which the patient experiences no articular symptoms whatever. These latent periods tend to become progressively shorter until acute episodes occur once or twice yearly, often with a certain regularity. Some patients, for unexplained reasons, are taken ill each spring and fall. At this stage of the disease, the patient is less likely to experience complete remissions and his illness is approaching or has entered on the phase of chronic gouty arthritis or chronic gout. In a few cases, most of which belong to the juvenile form, the disease is chronic from the outset. More frequently, a period of five to forty years separates the initial attack from the chronic phase.

In the advanced stages of the disease, an increasing number of joints are affected, particularly those of the feet, ankles and wrists and the knees and elbows. Subcutaneous tophi, representing infiltrations of urates into periarticular and bursal tissues, are frequently found and are responsible for the knobby deformities of the knuckles and interphalangeal joints. They may also be seen about the knee and elbow and along the tendons of the fingers, toes, ankles and wrists. Tophaceous deposits occur in nonarticular cartilage; indeed, their commonest site in chronic gout is the helix of the ear. They vary in size from a barely palpable nodule to deposits measuring as much as 5 cm. in diameter. Their presence in cartilage may be unattended by any symptoms, but in subcutaneous tissue visible inflammatory reaction usually results. There the deposits appear first as slightly red elevations that gradually develop into white, cream-colored or yellow nodules of varying size. The skin overlying a tophus may ulcerate and discharge a white, chalky material that on microscopic examination shows the characteristic acicular crystals of sodium urate. Such ulcerating lesions may occur anywhere on the body surface but are commonest on the hands and feet. They rarely become infected.

Tophi are found in about 50 per cent of all cases of gout. In some cases they antedate the acute joint disease, whereas in others they are not found until ten to thirty years after the initial attack. They should not be confused with the subcutaneous nodules of rheumatic fever and rheumatoid arthritis. Because they constitute the one pathognomonic lesion of gout, they should always be searched for. Regardless of whether or not a nodule has the characteristic clinical appearance of a tophus, it is unwise to accept it as such until it has been needled and the monosodium urate crys-

tals have been demonstrated or a positive murexide reaction has been obtained.

The term "irregular gout," still used by some writers, originally designated a group of nondescript symptoms that in the past has also been referred to as lithemia or as a uric acid, lithic acid, or gouty diathesis. The clinical markings of irregular gout were most varied and apparently incorporated all the inexplicable complaints that occurred in the gouty subject. Some of these were probably results of medication with impure preparations of colchicum. The term was, however, also applied to the indefinite ailment of members of gouty families who had never suffered an acute attack of gouty arthritis. In these cases the symptoms were often ascribed to an excess of uric acid proved by the finding of urate sediment in the urine! Neither this type nor an irregular type of articular gout postulated by some current writers[17, 18] deserves recognition. The patients described, usually women, exhibit none of the characteristic findings of symptomatic gout. Their arthritis is insidious in its onset and slowly progressive, without remissions or associated tophi. As a rule, these patients are advanced in years and show only a slightly higher than normal blood uric acid. In a few cases, hyperuricemia, probably due to nephritis, and rarely a family history of gout are found. If such variations of gout occur, they should be susceptible to pathological proof, and when present generally show favorable response to the therapy administered for acute gouty arthritis. The propriety of using such terms as "visceral" or "abarticular gouty" is equally dubious.

Premonitory Symptoms

The specific changes that presumably take place in the gouty subject between birth and the onset of the clinical illness have not been studied, but hyperuricemia has been demonstrated at an early age.[16, 19, 20] Whether it is ever present at birth is unknown, nor are bodily alterations immediately preceding the gouty seizure, the so-called "larval state," understood. Many patients experienced no premonition of the impending attack; some even feel their best at that time. Others complain of anorexia, nausea, indigestion, melancholia, stiffness, aching, polyuria and nocturia. The diuresis may be taken as an expression of the altered mineral metabolism, whereas the other prodromes remain unexplained.

Precipitating Factors

Considerable importance is generally attached to a number of factors said to precipitate an attack of arthritis in a patient with latent gout. Their true significance in relation to the disease has not been determined, and it is difficult to evaluate how often they are chance associations.

Minor or major trauma has long been considered the commonest precipitating factor. The prevalent involvement of the large toes has been attributed to the chronic strain on these articulations sustained in walking or from the pressure of ill-fitting shoes. Many similar examples of injury as an antecedent to gouty arthritis can be cited.

The belief that certain foods are promotive of gout is one of the oldest medical traditions and is still accepted by a majority of competent physicians. The proponents of this theory contend that the ingestion of purine-rich articles by the gouty subject results in an accumulation of uric acid in the blood, thus inducing an acute attack of gout. Habitual dietary excesses are considered to be predisposing factors, whereas periodic indulgence supposedly serves as a precipitating force.[12] It is a most regrettable circumstance that these teachings, which are shrouded in the semisanctity of a long and venerable heritage, have never been tested by either adequate experimentation or comprehensive statistical analysis of clinical data.

Because of the far-reaching practical importance of this question, the consideration of the relevant basic facts is recommended. Since predisposition to gout is inherited, it follows that dietary factors cannot be the cause of the disease. Although it is well proved that a high purine intake raises the blood uric acid content of a gouty subject, it has likewise been shown that neither hyperuricemia nor an elevated uric acid concentration in tissue fluids is by itself always sufficient to produce an attack of gouty arthritis, even in a predisposed subject. High-purine diets do not provoke the acute illness in latent gout with any regularity, and no correlation has been possible between the degree of hyperuricemia and the frequency, severity and duration of arthritis in gouty patients. It has been found that most gouty subjects do not show an adverse response to occasional excess-purine feedings, and that in well-controlled studies covering an extended period the frequency of seizures does not vary in alternating intervals of high-purine and low-purine intake. The incidence of gout among vegetarians is much higher than is usually assumed. The natural course of the disease is characterized by sudden changes in an erratic, unpredictable pattern. The temptation for both patient and physician to fasten the responsibility for these to some tangible factor is great, but the evidence quoted here should warn one against accepting as verified the influence of dietary habits on the development and progress of gout.

It has also been stated that certain foods, regardless of their purine content, are capable of produc

ing regular attacks in some gouty patients, supposedly as an allergic manifestation. A specific brand of cheese or wine or a particular kind of fruit or vegetable has been held responsible. Similar observations have not been reported by other investigators.

Attacks have been observed subsequent to the institution of a ketogenic[21] or high-fat diet. Lockie and Hubbard[22] proposed that the latter be used as a provocative test.

Some clinicians consider the ingestion of alcohol to be the most important of all precipitating factors. Fermented beverages are thought to be much more provocative than is distilled liquor. Others hold the mode of use a significant circumstance, considering that persons who overindulge in meat habitually partake of red wine and malt liquors, and therefore sustain the combined effect of two inciting agents. All are agreed that certain gouty subjects fare sumptuously with some regularity and that some of their attacks follow dietary and alcoholic indiscretions. This sequence, however, does not usually exist. For example, one of the patients at the Massachusetts General Hospital experienced only two attacks in twenty years, although his excesses continued throughout the symptom-free interval. Another suffered ten attacks in ten years during middle life but none during the subsequent fifteen years while his habits of eating and drinking remained unchanged. Cases of this description are by no means exceptional, and serve to emphasize that the instrumentality of alcohol in precipitating gouty arthritis is unproved. Actually, chronic alcoholics[23] have been said to show no higher and teetotalers no lower than the average incidence. Only the collection of accurate data from a significant number of cases will give the final answer.

Attacks of gouty arthritis are said to have followed the intramuscular administration of liver extract and of salyrgan, ergotamine tartrate, insulin, decholin, thiamin chloride and other medicinal agents. The case reports are too sparse to allow a conclusion as to cause and effect.

Hench[24] has repeatedly stressed that gout should be suspected when arthritis occurs during the first seven days following a surgical procedure, but the exact incidence of postoperative gout is unknown.

Coincidental diseases such as leukemia, polycythemia and chronic glomerular nephritis, as well as marked blood loss and transfusions, are said to have activated latent gout. Furthermore, severe purgation, foreign-protein therapy, exposure to cold and dampness and emotional upsets have been accused of producing attacks.

Complications

As stated previously, premature vascular disease and the anatomic and physiologic alterations resulting therefrom constitute the important complication of gout. Some earlier writers[7, 23] have stressed the high incidence of venous thrombosis, a finding that has been rare in my experience.

The appearance of persistent albuminuria and casts usually marks the beginning of a vascular nephritis that may ultimately prove fatal. The majority of gouty patients die from uremia. Because of the frequency with which nephritis occurs in gout, Hench[25] states that chronic arthritis associated with distinct renal impairment suggests gout until proved otherwise. Some writers speak of secondary gout caused by chronic nephritis, other renal disease or leukemia. Such cases probably represent latent gout complicated by other diseases associated with hyperuricemia. Under these conditions, it is important to obtain a detailed family history and, if possible, blood uric acid determinations on the patient's relatives.

The incidence of urinary calculi in gouty subjects is relatively high, amounting to 12 per cent in Hench's[25] series. An occasional patient experiences one or more bouts of renal colic prior to the first gouty seizure. Arthritis in connection with urinary lithiasis should always suggest the presence of gout. No sound theoretical explanation for the frequent association of the two conditions is known, nor has the incidence of urate stones been determined.

Previously gout was assumed to be prevalent among lead workers, hence the term "saturnine gout." It, too, was considered an example of secondary gout due, in this instance, to the vascular nephritis of plumbism. Whereas gout is more rarely a complication of lead poisoning than was previously assumed,[26] it may of course be associated by chance with the vascular nephritis of plumbism. Other types of arthritis occurring in a patient with hyperuricemia due to renal damage from lead poisoning may in the past also have been erroneously diagnosed as gout.

Episcleritis due to urate deposits occurs rarely.[5, 15] Eczema and various other complications are no more frequent than in all persons of comparable age and are probably unrelated to gout.

Diagnosis

The diagnosis of joint diseases is in most cases relatively easy when based on a detailed medical history and a complete physical examination. A few well-chosen laboratory tests or a therapeutic trial with specific medication are often valuable adjuncts. Biopsies may be necessary. The passage of time and further observation are indispensable.

Clinical Findings

A history of recurrent attacks of acute arthritis separated by completely asymptomatic intervals should always suggest gout, particularly in a

middle-aged man. Provided the presence of the disease is suspected, confirmation in most cases is relatively simple. The abrupt onset of severe articular pain, usually without known cause, followed rapidly by a red, hot swelling of the joint, extending beyond the articular margins, is of great diagnostic significance, especially in a first attack. Additional aids are a positive family history, positive identification of tophi and the occurrence of cuticular desquamation as the edema subsides, a finding highly characteristic of gouty arthritis. The dramatic response to full doses of colchicine, rarely observed in any other types of arthritis, is of real diagnostic significance.

Laboratory Findings

Hyperuricemia is an almost invariable feature of the disease. Its presence, therefore, if not attributable to other causes, constitutes evidence of prime importance. The serum uric acid values are rarely lower than 6 mg. per 100 cc. In the few exceptions, less than 2 per cent, they vary between 5.2 and 5.8 mg.

For the determination of uric acid, one of two methods, that of Folin[27] or that of Benedict,[28] should be employed. Both depend on the reduction of complex tungstate reagents to colored compounds. This reaction is not strictly specific for uric acid and may be enhanced or inhibited by unrelated substances present in the blood. *While neither test offers undue technical difficulties, only the greatest care in preparing the reagents and frequent control determinations assure reliable results.* The use of serum is preferable to that of whole blood. Since the distribution of urates between the plasma and the cells is a function of the bicarbonate content, specimens should be collected and centrifuged under oil if the greatest accuracy is desired. Folin's[29] method for unlaked blood is free from the objections to the other whole-blood methods, but since it is doubtful whether diffusion of urates from the cells is ever complete, the method should not be used if sufficient blood can be obtained for a determination on serum.

No characteristic change in serum uric acid occurs immediately prior to an acute attack of gouty arthritis. In some cases it remains unchanged; in others it may be increased or decreased. *In order to avoid erroneous interpretations, particularly of response to therapy, it is extremely important to appreciate that the blood uric acid level is inconstant and that cyclic changes occur at irregular intervals.* In one case variations between 7.4 and 14.5 mg. per 100 cc. were observed that could not be attributed to any known cause and were in no way related to the incidence of arthritis.[30] Various tests[31] designated to measure the urate-concentrating power of the kidney are neither entirely satisfactory nor necessarily of diagnostic value in gout.

Analyses of joint effusions in gouty arthritis reveal uric acid concentrations in the synovial fluid similar to those in serum[15]; the same is true for sugar. The viscosity is reduced and the protein content increased. The total leukocyte counts may vary from 1000 to 31,000, with polymorphonuclear leukocytes ranging from 50 to 95 per cent.

Patients with acute gouty arthritis generally have a mild to moderate leukocytosis. The mononuclear count is frequently increased. The sedimentation rate may be elevated. In several cases at the Massachusetts General Hospital the rates were as high as 2 mm. per minute (the upper limit of normal being 0.4 mm. per minute[32]). Evidence of mild renal impairment is commonly met with. Achlorhydria occurs no more frequently in gouty patients than in other persons. An abnormal sugar-tolerance curve, occasionally present, is of no diagnostic significance.

Roentgenographic Findings

The roentgenographic findings most suggestive of gout are well-defined, punched-out areas, usually 5 mm. or more in diameter. They are most commonly observed in the subchondral bone at the bases or heads of the phalanges. The feet are apt to show these lesions even in cases in which they have never been affected clinically. Such changes may appear late in the disease; for example, 19 per cent of the patients in one series had had gout for twenty-eight years or longer and exhibited tophi and hyperuricemia in every case, yet failed to show subchondral lesions roentgenographically.[25] The frequency with which these defects, the result of urate deposition in bone, are found is directly related to the severity of the disease. They may be demonstrable in the region of joints not commonly affected—for example, in the neighborhood of the sacroiliac joint. They should be distinguished from the circumscribed areas of rarefaction seen in degenerative joint disease and rheumatoid arthritis. Similar findings may be produced by the gummas of syphilis and by leprosy and yaws, as well as by tuberculosis and Boeck's sarcoid. Occasionally tophaceous deposits result in bone expansion with or without destruction, thus simulating roentgenographically a bone tumor. In addition to such abnormalities, one may find thickening, joints of soft tissues, narrowing of conspicuous marginal overgrowth and marked destruction of the articular surfaces.

Decalcification occurs in a few patients who have suffered prolonged, severe attacks involving the small joints of the feet and wrists. In these exceptional cases, the marked decalcification, joint destruction and obvious ankylosis closely approximate the changes seen in specific infectious or rheumatoid arthritis. Premature arteriosclerosis

is frequently demonstrable in the vessels of the legs and feet.

Although the x-ray findings in gouty arthritis are characteristic and consistent, they cannot be considered specific. The roentgenologist's impressions should therefore be taken only as a corroboration of a clinical diagnosis.

Provocative Tests

Experience with provocative tests at the Massachusetts General Hospital has been most disappointing, whether these were applied immediately after an attack or during a remission. This has been true of a high-purine (2.5 to 3 gm.) diet or a high-fat (250 to 300 gm.), diet or of large amounts of port wine administered singly or in combination with the diets. Failure to precipitate an attack with any regularity has led to abandonment of these tests as diagnostic aids.

Differential Diagnosis

Occasionally gouty arthritis is confused with traumatic joint disease, cellulitis, rheumatic fever, one of the specific infectious arthritides, rheumatoid arthritis, Heberden's nodes or acute bursitis, particularly when the last is associated with a hallux valgus deformity.

Traumatic arthritis is as a rule readily diagnosed. Articular pain and swelling follow almost immediately on a known injury. Marked inflammatory reaction of the periarticular tissue is not discernible, and the symptoms always remain confined to the affected joint. The patient exhibits none of the characteristics of the gouty subject and his arthritis never responds to colchicine therapy. It should be remembered, however, that trauma may mark the onset of acute gout as well as that of infectious arthritis. In such cases differentiation is greatly aided by aspiration and analysis of the joint fluid. An acute traumatic effusion contains rarely more than 1000 leukocytes per cubic millimeter and polymorphonuclear leukocytes ranging from zero to 20 per cent, in contrast to the higher values usually found in the other acute arthritides.[15]

Cellulitis or septic inflammation is frequently suspected; in fact, it is sometimes diagnosed before it has become evident that one is actually dealing with acute gouty arthritis. Occasionally, the affected joints have been incised and drained. One can readily appreciate the diagnostic difficulties offered by a patient who presents himself with a painful, red, hot swelling of the dorsum of the hand or foot, with or without lymphangitis and fever. Failure to find a skin abrasion or other portal of entry for an invading organism and careful elucidation of the past history generally lead to the correct diagnosis.

Rheumatic fever, especially in young patients, can be simulated by recurrent attacks of gouty arthritis. The clinical differentiation, however, should not be difficult. The arthritis of rheumatic fever usually follows an upper respiratory infection or other precipitating factors by seven to fourteen days. Patients frequently exhibit weight loss, nosebleeds, skin eruptions, subcutaneous nodules, tachycardia and precordial pain. The electrocardiogram often shows a prolonged PR interval and other alterations. The ultimate development of valvular heart disease is of the utmost diagnostic importance.

Specific infectious arthritis, due to a pyogenic organism, in the acute phase more nearly resembles acute gouty arthritis than it does any other type of joint disease, particularly since it is occasionally recurrent. In such cases, usually caused by the gonococcus, the clinical picture shows some similarity to that of gout, as in a patient who entered the Massachusetts General Hospital suffering from his eighth attack of arthritis. He stated that recovery from the previous seven seizures had been complete. Differentiation was facilitated by a history of a genitourinary infection and such constitutional symptoms as chills and fever preceding in close parallelism every exacerbation of arthritis. Although the inflammatory swelling of specific infectious arthritis may be severe, it is rarely so marked or occurs so precipitously as does gouty arthritis. Particularly with the aid of synovial-fluid findings, one should not encounter serious diagnostic difficulties.

Typical rheumatoid arthritis ushered in by constitutional, vasomotor and neurologic symptoms, of insidious onset and characterized by symmetrical joint involvement, should rarely if ever be mistaken for gouty arthritis. In 18 per cent of all cases, however, rheumatoid arthritis is marked by an atypical onset, and in 7 per cent it may remain atypical for a long time. In this form, an apparently healthy person experiences an acute attack of arthritis without prodromes, preceding acute illness or an obvious focus of infection. The joint involvement may be polyarticular, migratory or, occasionally, monoarticular. Recovery from the first attack is often complete, and the remission may last for a few months or even for years. The patient may have a number of attacks before the disease becomes chronic. Careful clinical observation and determination of the blood uric acid concentration facilitate the distinction between the two diseases.

The clinical features of chronic gout with ankylosis may resemble even more closely those of rheumatoid arthritis. Two such cases have been seen at the Massachusetts General Hospital in a

relatively early stage of the disease, and others have been reported.[4, 23] In one,[30] the onset of gout at twenty-one years of age was followed by chronic arthritis within five years. Widespread ankylosis was demonstrable at the age of twenty-eight. The diagnosis of gout was confirmed by the identification of sodium urate crystals in tophi of the ear and in the fingers, olecranon bursa and tissues of four joints. Of particular interest were the findings in the astragalotibial joint. Extensive pannus formation, responsible for complete fibrous ankylosis, simulated strikingly the gross pathologic changes of rheumatoid arthritis. Even the microscopic appearance of the synovial tissues might have been difficult to distinguish definitely from the chronic inflammatory lesions of rheumatoid arthritis, except for innumerably small urate foci. Such unusual forms of gouty arthritis are admittedly rare. They should not be confused with rheumatoid arthritis. Clinical differentiation is greatly aided by a painstaking inquiry into the past and family histories. Biopsies of nodules, tophi and synovial tissues often lead to the correct diagnosis. Analysis of the synovial fluid may or may not help to distinguish one disease from the other. The association of the two is extremely rare. A few cases have been reported, but their authenticity is questionable.

Bursitis, particularly as a manifestation of a hallux valgus deformity, has probably on innumerable occasions been mislabeled as gouty arthritis. This diagnostic error can be avoided if the infected part is carefully examined. The swelling is limited to the bursa and the immediately adjacent tissues, and the distended sac may be easily palpated. Motions of the metatarsophalangeal joint are painless within a limited range.

Heberden's nodes, classic stigmas of degenerative joint disease, consist of hypertrophic osseous changes at the articular margins of the terminal interphalangeal joints. They are insidious in development and not usually productive of severe symptoms, and may be readily differentiated from tophaceous deposits in the skin and deeper tissues surrounding these joints. Occasionally, however, Heberden's nodes are acute in onset and are then frequently confused with gouty arthritis. The distal finger joints may be painful, reddened, bulbous, fluctuant and extremely tender. Numbness and tingling of the involved fingers may also be complained of. Heberden's nodes occur predominately in women and affect the index and middle fingers oftener than the other phalanges. Tophi, common in men and rare in women, are discernible by their yellowish color. It is well known, of course, that the two disorders may be associated coincidentally or casually.

Summary

The varied manifestations of gout are reviewed in detail to reacquaint physicians with the disease. If this treatise serves its purpose, there should result more correct diagnoses and fewer therapeutic errors.

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Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29401

PRESENTATION OF CASE

A fifty-one-year-old storekeeper was admitted to the hospital because of chest pain.

The patient was well until about five years before admission, when he noted the gradual onset of intermittent, substernal pain. The pain was variously described as being in the middle or just to the left of the sternum at the level of the third, fourth and fifth ribs and at times radiating to the left arm. It was unrelated to food, exercise or emotion but was sometimes intensified by deep inspiration. It lasted for a few minutes and was often followed by a feeling of discomfort for two or three hours. Sitting down occasionally relieved the pain. During the course of the next few years the pain increased in frequency and severity, so that on entry it was described as a dull, heavy sensation beginning at the lower end of the sternum, radiating to the left chest and occasionally to the left arm as far as the elbow, leaving the arm numb and heavy. The pain seemed to come on ten or fifteen minutes after he arose in the morning, persisted all day and went away one or two hours after he retired at night.

During the year or two before admission, the patient had had "considerable gas in his stomach" following meals, which was relieved by belching. There were some lower abdominal cramps and diarrhea without blood or mucus for a period of four or five weeks. He was seen by various physicians one of whom had performed gastrointestinal and gall-bladder x-ray studies and had told him that he had "colitis" and a misshapen gall bladder. The diarrhea ceased, but the abdominal discomfort continued. It was sometimes relieved by soda or a glass of whisky, and at times aggravated by eating.

About six months prior to entry, the patient developed a severe cough and wheezing dyspnea. He lost his voice for a short time. The cough was "tight" and worse in the mornings. On one occasion he raised bright-red sputum every morning for about a week. At other times however, the sputum, which was copious in the mornings, was whitish to brownish but not foul. It seemed to increase with exertion. During that time, he felt tired but had no chills, fever or night sweats. He had lost 10 to 20 pounds in the course of the year and a half preceding entry. His appetite had remained fair, and he was able to eat "nearly everything." There was no vomiting, dysphagia or diarrhea, but he had had a feeling of nausea occasionally at night. The patient had no orthopnea but slept on two pillows to prevent coughing. He had noted the gradual onset of dyspnea on exertion, which persisted. For the two months before admission he had received two digitalis capsules daily, without improvement. All his symptoms were variously described as progressive or intermittent, with periods of remission and exacerbation. There was no history of aspiration of a foreign body or of operation on the nose, mouth or pharynx.

Physical examination showed a slightly obese man in no distress. The anteroposterior diameter of the chest was increased with somewhat diminished respiratory excursions, which seemed to be mainly diaphragmatic. The left half of the diaphragm was slightly higher and moved less than the right half. One or two observers noted a questionable dullness with diminished tactile fremitus and breath sounds at the left base, whereas two or three others thought that the lungs were clear. The left border of cardiac dullness was 10 cm. to the left of the sternum. The sounds were of good quality and regular. The aortic second sound was greater than the pulmonic. There were no murmurs. The examination otherwise was negative.

The blood pressure was 125 systolic, 85 diastolic. The temperature was 98.6°F., the pulse 84, and the respirations 32.

The blood showed a red-cell count of 5,730,000 with a hemoglobin of 18.5 gm. The white-cell count was 10,300, with 60 per cent neutrophils. The urine was normal. The stools were guaiac negative. A blood Hinton test was negative. The blood protein was 7.3 gm. per 100 cc. A Graham test was negative. An electrocardiogram revealed a rate of 90, a PR interval of 0.14 second and slight axis deviation. The T waves in Leads 1, 3 and 4 were low, and T_4 was slightly diphasic. X-ray examination of the chest showed a mass behind the heart on the left side with sharp medial and anterior borders, apparently corresponding to a collapse of a large portion of the left lower lobe. The left hilus was slightly smaller than normal. There was no respiratory shift of the mediastinum. The heart was normal in size and shape. A gastrointestinal series showed the esophagus crossing the mass in the left lower chest without being attached to it. On re-examination, however, a herniation of the cardiac portion of the stomach

*On leave of absence.

through the diaphragm was noted (Fig. 1). The stomach was apparently curled on itself as it passed through the opening so that only with the

FIGURE 1. *Roentgenogram following Barium Meal. Note the hiatus hernia and the round mass above the fundus of the stomach.*

head depressed and the patient lying on his back was the entire supraphrenic mass filled with barium. A barium enema was negative. There was no evidence of herniation of the large bowel through the diaphragm. The splenic flexure approached the diaphragm somewhat more closely than usual and moved freely with respiration.

During the first few days after admission the patient had several attacks of coughing, as well as a slight dull pain just to the left of the lower end of the sternum and considerable gas pain.

An operation was performed on the eighteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. STRIEDER*: Perhaps we might see the x-ray films first. I should particularly like to see the film that was described in the history, but in which I could not find or recognize the shadow noted on the left side "with sharp medial and anterior borders, apparently corresponding to a collapse of a large portion of the left lower lobe.

DR. LAURENCE L. ROBBINS: This presumably is the solid mass described in the lung, and these air bubbles represent the hernia. I should say that this line demonstrates what they were trying to bring out for the medial margin of the lesion in the chest. So far as the spot film is concerned, this is the esophagus, and this the stomach; there still appears to be an area of increased density above the fundus. I do not believe that the splenic flexure is abnormal in position in the film of the colon.

DR. STRIEDER: Do you think you can see in any of the films an area that is consistent with a collapsed portion of the left lower lobe?

DR. ROBBINS: I cannot see a definite area of collapse. There is an area in the left lower lobe

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in which there is no air. I should think that this was its margin, with the hernia below it, because one can see a bubble. This film again shows a gas bubble in the herniated portion of the stomach. It is perfectly possible that the mass above it is in the lung.

DR. STRIEDER: Are you impressed by the pulmonary shadow itself?

DR. ROBBINS: I do not know exactly what to say. It is quite a sharply defined shadow for a hernia and it certainly seems to be surrounded by air, which would make one think it was within the lung or against the pleura.

DR. STRIEDER: We have a fifty-one-year-old man on whom an x-ray diagnosis of esophageal hiatus hernia of the stomach had been made. As I looked this over, I thought I could reconcile the symptoms with the x-ray diagnosis, which is often dangerous. There are several aspects that do not fall in line, however, and perhaps I shall devote a moment or two to these as I come to them.

In the first place, symptoms of five years' duration in a fifty-one-year-old man are not unusual for esophageal hiatus hernia or for any type of diaphragmatic hernia. Although the hernia may be present at birth, the symptoms may not occur until the patient is well along in years. It is interesting that the first diagnosis by x-ray of esophageal hiatus hernia was made at the Mayo Clinic in 1921. In 1940, Harrington* published a series of 250 cases of diaphragmatic hernia, of which 198 were paraesophageal in type. So it is by far the commonest type of diaphragmatic hernia recognized.

The pain that was variously described as being in the middle or just to the left of the sternum, radiating to the left arm, is explainable, in so far as pain in the arm is concerned, on the basis of phrenic reference due to diaphragmatic spasm. In diaphragmatic hernia, pain commonly simulates that of angina, or at least is thought to simulate that of angina. Patients may complain of severe pain in the arm in connection with their thoracic pain. Classically, paraesophageal hernia pain radiating through to the back and to the left of the spine is usually lower, but any patient may have a variety of symptoms depending on the type of hernia, the quantity of viscus herniated and the type of viscus herniated.

"Sitting down occasionally relieved the pain." That is contrary to the usual story. Most patients with esophageal hiatus hernias are relieved when they stand up or are propped up in bed because the upright position tends to reduce the hernia, if it is reducible.

*Harrington, S. W. Diagnosis and treatment of various types of diaphragmatic hernia. *Am. J. Surg.* 50:381-446, 1940.

"During the year or two before admission the patient had had 'considerable gas in his stomach' following meals, which was relieved by belching." This again is classic for diaphragmatic hernia. There is trapping of air above the diaphragm, causing considerable distress, and relief by belching. Consequently many erroneous diagnoses are made. Cholecystitis is a diagnosis often made when the patient's symptoms are entirely due to diaphragmatic hernia.

I cannot explain the lower abdominal cramps and diarrhea on the basis of gastric herniation alone. It is possible that at the time of these episodes the patient may have had a portion of the colon in the hernial sac, although that was never demonstrated in the films. "The diarrhea ceased, but the abdominal discomfort continued. It was sometimes relieved by soda or a glass of whisky, and at times aggravated by eating." That again is unexplainable, but apparently homely remedies do wonderful things for patients. The fact that the pain was relieved by whisky reminds me of a physician of this hospital whose symptoms were relieved by whisky although he had an ulcer of the stomach that was about to perforate when demonstrated at operation. Of course, the relief from soda seems reasonable. Patients with hernia through the diaphragm have distress because they regurgitate gastric secretions into the lower esophagus, and ulceration of the lower esophagus frequently occurs on the basis of prolonged, continued regurgitation. They often have ulceration of the stomach from the pressure of the hernial orifice on the wall of the stomach. This may give rise to hematemesis or to frank blood, or more commonly occult blood, in the stools.

"About six months prior to entry, the patient developed a severe cough and wheezing dyspnea. . . . On one occasion he raised bright-red sputum every morning for about a week." That is the ruby-hued herring that upsets our tight little argument. I have never seen a patient with diaphragmatic hernia who coughed up blood, and I find no reference to this in the 198 cases that Harrington observed at the Mayo Clinic. It is entirely conceivable, however, that the cough, dyspnea and other respiratory symptoms are explainable on the basis of hernia. We know that there is a certain amount of diaphragmatic spasm and crowding of the lung by the hernia if it is sufficiently large, which will result in shortness of breath and even wheezing. The site of the hernia makes it seem unlikely, at least to me, that the hernia could have so encroached on the lung that there was actual distortion of the bronchus to account for the cough and bloody sputum. There is no mention of bronchoscopy. If the pulmonary

symptoms had been of significance I think it would have been suggested and perhaps carried out. It would have been interesting to know about it, at any rate. The other alternative, of course, is to consider whether the patient vomited the bright-red blood, rather than coughed it up, which would fit nicely into the picture, but would not explain the prolonged cough and the copious sputum unless they were caused by the emphysematous changes of advancing years.

A weight loss of 10 to 20 pounds can well occur in a patient with esophageal hiatus hernia. These patients develop a "food fear" and because of this fear or the inability to take food they lose weight. The patient stated that he was able to eat nearly everything, but closer questioning might have elicited the fact that he was on a reasonably restricted diet. There is no question that there is such a thing as a so-called "stomach cough," which we heard a great deal about years ago in the early days of sanatoriums and is still spoken of in tuberculosis institutions. Many tuberculous patients on prolonged bed rest have gastric symptoms related to hyperacidity, and with it they have a cough that is relieved when the hyperacidity is controlled. I am convinced that coughing in such cases is some sort of a reflex phenomenon since we see it clinically so often.

"All his symptoms were variously described as progressive or intermittent, with periods of remission and exacerbation." That again is typical of hiatus hernia. These patients may be perfectly well for months, during which time the stomach is in normal position. The prolonged symptoms are probably due to the adherence of the stomach in the hiatus, or its being retained there for a period of time. The patient had no history of aspiration of a foreign body or anything else to make us suspect a suppurative lesion in the lung that caused cough.

The stools were negative, although commonly with diaphragmatic hernia the stools are positive for blood because of prolonged bleeding from an erosion of the stomach, which often results in secondary anemia. Which brings me down to the point where I must make a diagnosis.

Was a bronchoscopy performed?

DR. BENJAMIN CASTLEMAN: No.

DR. STRIEDER: I do not see how I can go any farther than to say that this patient had a diaphragmatic hernia. I am not very much impressed, and I gather that Dr. Robbins is not, by the pulmonary shadow. I think that the shadow might have been due to compression of the lung.

DR. ROBBINS: Now that I have had more time to look at the gastrointestinal film, I believe that I can see a round mass above the barium-filled fundus of the stomach.

DR. STRIEDER: It is not part of the hernia?

DR. ROBBINS: I do not believe so, since it is more or less completely surrounded by air, and apparently is separate from the upper limit of the fundus of the stomach.

DR. STRIEDER: There is room for all sorts of conjecture. I cannot explain the hemoptysis on the basis of anything that we have to go on except the possibility, as Dr. Robbins has pointed out, of tumor in the lung. Given an x-ray diagnosis of a tumor in the lung, there is a certain differential diagnosis that one can go through, but actually it resolves itself into a more or less philosophic discussion concerning the exact histopathology, and the pathologists often surprise us when they tell what it is. If we can accept this shadow as evidence of a pulmonary tumor, then we have to make such a diagnosis. However, I think I shall be brash, fly in the face of the X-ray Department and refuse to be impressed by it, although that may be a serious error. Probably all these symptoms can be explained on the basis of diaphragmatic hernia of the paraesophageal type.

CLINICAL DIAGNOSIS

Esophageal hiatus hernia.

DR. STRIEDER'S DIAGNOSIS

Esophageal hiatus hernia.

ANATOMICAL DIAGNOSES

Esophageal hiatus hernia.
Bronchiogenic cyst of lung.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Robert K. Brown operated on this patient. Since he is not here I shall read part of his operative note:

> Under intratracheal ether anesthesia, a long, curved, posterolateral incision was made over the left ninth rib, and approximately 35 cm. of this rib was subperiosteally resected. Free pleural space was entered. There was a herniation in the posterior leaf of the diaphragm about 7 cm. in diameter. This was somewhat adherent to the lower lobe of the left lung. As the adhesions were separated and the lung mobilized from the diaphragm, it was found that, on the medial aspect of the basal segment of the lower lobe, a rounded, tense, 4-cm. mass presented. This seemed to be connected to a cystic mass that occupied most of the basal segment of the left lower lobe. Running from it through the diaphragm between the hernia and the esophageal hiatus were two good-sized vascular structures, one about 2 mm. in diameter, and the other about 5 mm. in diameter and rather thick walled. These were dissected free, doubly ligated and cut. They turned out to be veins, the larger having a mural thrombus in its lumen. The remainder of the basal lobe was readily freed.

It was then apparent that there were two lesions—the diaphragmatic hernia, which was easily reducible, and the cystic tumor in the lower lobe, which was thought to be a bronchiogenic cyst. It was decided to repair the hernia and remove the cyst. Since segmental lobectomy is not an absolutely clean procedure, it was also decided to repair the hernia by imbrication without opening the diaphragm. This was done, and a good approximation of normal strong diaphragm was obtained, the suture line running posterolateral in a radial direction. Mass removal of the basal segment of the left lower lobe containing the tumor was carried out.

FIGURE 2. *Photograph of Bronchiogenic Cyst.*

The specimen that we received was a segment of lung containing the large cystic mass that Dr. Brown was able to feel. After fixation, section of the mass revealed a large cyst filled with gelatinous fluid (Fig. 2). Microscopic examination of the cyst wall showed it to be lined with ciliated bronchial epithelium and to contain foci of smooth muscle and cartilage. It was therefore a true bronchial cyst within the lung. Most people believe that these cysts are congenital in origin—in other words, that in the embryologic development of the lung one of the lung buds fails to develop and the bronchial secretion is unable to get out. Although we were unable to find any communication with a large bronchus, I imagine there must have been one with a small bronchus; otherwise the patient would not have coughed up blood. There was no inflammatory reaction around the lesions. Such absence of infection is often used as an argument against the theory that lung cysts originate from ordinary bronchiectasis. Most lung cysts are certainly of bronchial origin.

Although the preoperative diagnosis was hiatus hernia, there were several men who continually asked the X-ray Department whether this lesion was in the lung.

DR. ROBBINS: With reason, I should say.

CASE 29402

PRESENTATION OF CASE

A sixty-three-year-old tobacco farmer was admitted to the hospital because of pain and weakness in the right arm.

The patient had been in apparent good health until about ten months before entry when he noted pain and weakness of the upper arm that bothered him while working. The pain increased in severity until seven months before entry, when it occurred at night and was relieved by letting the arm hang down. Chest roentgenograms at a community hospital about four months before admission were said to have shown a mass in the right upper chest. He was given a course of seven x-ray treatments over a month's time with apparently no decrease in the size of the mass. While receiving the x-ray treatments he had a paroxysmal nonproductive cough, which cleared after treatment. The pain and weakness in the arm increased in severity. The pain was in the lateral aspect of the right deltoid region, the bi-

ceps, the extensor surface of the forearm and the right ring finger. It was aggravated by lifting and by certain positions in bed. In the month before entry he developed a deep soreness in the right side of his neck. There was no weight loss, anorexia, hemoptysis, dyspnea, orthopnea, headache, giddiness or changes in the voice.

At twelve years of age "a large swelling of the neck had been drained through a midline incision." He had had typhoid fever at twenty. About twenty years prior to admission it was discovered that he had diabetes, which was controlled by diet without insulin.

Physical examination showed a weatherbeaten man in no distress. Both pupils were small and reacted to light and accommodation. The trachea was deviated to the right. No masses or lymph nodes were palpable. There was tenderness to deep pressure over the muscles in the posterior triangle of the neck. The chest was barrel shaped. The heart and lungs were normal. The shoulder motions were normal except for limitation of outward rotation of the right arm. There was no noticeable atrophy, masses, hyperesthesia, numbness or vascular changes.

The blood pressure was 110 systolic, 70 diastolic. The temperature was 98.6°F., the pulse 70, and the respirations 20.

The blood showed a red-cell count of 5,140,000, with a hemoglobin of 15.3 gm. The white-cell count was 4200, with 75 per cent neutrophils. The urine showed a + test for albumin, but was otherwise normal. The blood sugar was 94 mg. per 100 cc.

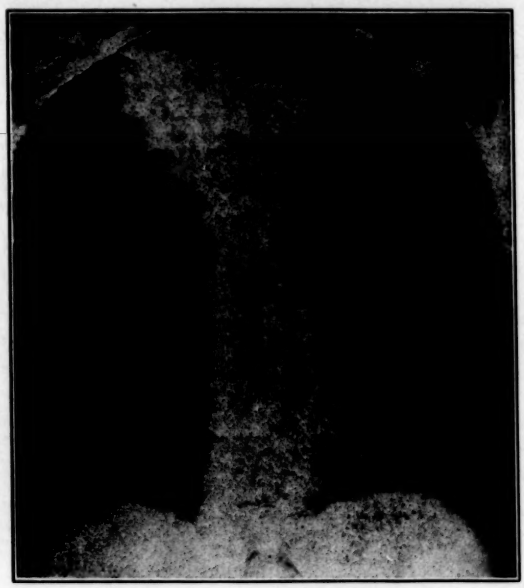

FIGURE 1. *Roentgenogram of Chest.*
The mass in the right superior mediastinum lies between the trachea and esophagus. There is slight extension to the left, above the aortic arch.

X-ray examination of the chest showed a mass arising from the upper mediastinum and lying between the trachea and esophagus (Fig. 1). The mass measured approximately 13 by 13 cm. It was largely on the right side but there was apparent extension to the left. It was attached to the trachea, which was displaced to the left and posteriorly. It was probably attached to the esophagus in the region of the aortic arch. There were no pulsations. The mass appeared to change its

shape on deep inspiration and slightly on changing position. There was no shift of the mediastinum. The lungs were normal. The heart was slightly enlarged in the region of the left ventricle. The aortic arch was prominent. The diaphragm showed normal respiratory motions. The visualized bones appeared normal.

On the fifth hospital day a mediastinal exploration was performed.

Differential Diagnosis

Dr. Reed Harwood: Our problem is a discussion of a mass in the chest and the nerves involved by this mass.

Taking the second part first, the nerves involved appear to be the medial brachial cutaneous and the intercostohumeral on the medial side of the biceps.

These are supplied by the first and second thoracic nerves. The dorsal antibrachial cutaneous and the medial antibrachial cutaneous are the sensory nerves of the dorsum of the arm. The first of these is supplied by the fifth to the eighth cervical, and the second by the eighth cervical and the first thoracic. The ulnar nerve, which is the one involved so far as the finger is concerned, is supplied by the eighth cervical and the first thoracic. The area over the deltoid region is supplied by the supraclavicular nerve, which comes from the third to the sixth cervical nerve. It is hard to explain on the basis of a chest tumor how the patient had so much pain over the deltoid region since these nerves arise outside the thoracic cage. Similarly, the description of weakness of the arm and limitation of motion of the shoulder joint, particularly on outward rotation, I cannot explain on the basis of a lesion in the chest, because these muscles are supplied by nerves higher in the cervical region.

I shall discuss the mass that was drained at the age of twelve. I suppose that it was a thyroglossal cyst and not connected with the present illness, unless we can reason that a patient who had one embryonic rest is apt to have another elsewhere.

There are two discrepancies that I want to point out. The first is that in the physical examination the trachea was said to deviate to the right, and in the x-ray description the trachea was said to deviate to the left. The other discrepancy is that the record states at one point that the tumor arose between the esophagus and trachea and at another point that the tumor had pressed the trachea backward as well as to the left. I am going to ask Dr. Robbins to straighten me out on these two points. It does not seem possible for a tumor arising between the trachea and esophagus to press the trachea posteriorly.

Dr. Laurence L. Robbins: If the record states that the trachea was deviated to the left, it is incorrect. I remember the case very well. The trachea was in the midline and was displaced anteriorly; the mass lay between the trachea and esophagus and pressed against both. It was attached to the trachea because the mass moved each time the patient swallowed.

This is the mass, chiefly on the right but with extension to the other side. The mass was smooth so far as could be determined from the films. As I said before, it was in the midline and pushed the trachea anteriorly, not posteriorly.

Dr. Harwood: The mass is said to have changed in position.

Dr. Robbins: That may have been a faulty observation. I examined the patient and was convinced at the time that the mass changed its shape with changes in his position.

Dr. Harwood: Dr. Robbins evidently thought it was a cyst before operation and is now not quite so sure.

Dr. Robbins: That was my impression.

Dr. Harwood: There are a number of masses in the chest that I am going to exclude before considering tumors of the mediastinum. Tuberculosis and empyema can be excluded on the basis of the history. Lung tumor can be excluded because of the absence of cough and hemoptysis. Thymoma can be excluded because such tumors arise in the anterior mediastinum, and there is no evidence of myasthenia gravis. I am going to exclude lymphoma because of apparent lack of response to x-ray treatment. Because there was no tracheal tug or vascular phenomena in the arms, aneurysm seems unlikely, but one should be sure that the Hinton test was negative.

Dr. Benjamin Castleman: The Hinton test was negative.

Dr. Harwood: Malignant disease can be excluded less certainly, but I am inclined to think that this was not a malignant tumor, principally because the tumor was perfectly round and there were no constitutional symptoms, such as weight loss. However, I cannot exclude the possibility of a benign tumor that had become malignant.

In considering mediastinal tumors I shall mention the esophagus first. A tumor of this size in the lumen or in the wall of the esophagus would certainly cause dysphagia, which this patient did not have. Of the cystic embryonic rests, dermoid cyst is one of the more frequent ones, but it usually arises in the anterior mediastinum and often areas of calcification are seen in the x-ray films. I think it is not likely that this was a dermoid cyst. Bronchiogenic and tracheal cysts are both good possibilities. The location is correct, and such tu-

mors may be soft. A solid embryonic rest, such as a teratoma, is usually irregular in outline and shows areas of calcification. Regarding tumors of neurogenic origin, von Recklinghausen's disease may present a single tumor arising in the neural canal. This usually produces erosion of the articular facets of the vertebras in that region, but I take it that such a lesion was not present here. Furthermore, there were no other neurofibromas noted on physical examination. A single neurofibroma of the mediastinum is another possibility. They usually arise in the posterior mediastinum and produce erosion of the ribs.

Finally, we should consider the possibility of substernal goiter. Against this is the fact that there were no masses in the neck. Most substernal goiters, not all of them, are attached to the lower pole of the thyroid. Furthermore, 90 per cent are seen in front of the trachea rather than behind it. So there is a 10 per cent chance, anatomically speaking, that it was in the correct position. In substernal goiter the enlargement is preponderant on one side and the trachea is deviated to the opposite side. The deviation begins at the hyoid bone and obtains maximal deviation at the widest part of the tumor. Since in this case there was no deviation of the trachea, I am going to say that this patient did not have substernal goiter. I am therefore led to the conclusion that he had a cyst of the trachea, possibly a bronchiogenic cyst, and that is my final diagnosis.

DR. JOST MICHELSEN: Were there no x-ray films of the cervical spine?

DR. RICHARD H. SWEET: I do not recall. At any rate, none were taken here. He had been studied extensively at a good clinic in Connecticut. His presenting symptom then was pain in the arm and shoulder girdle. There was no suspicion of a mediastinal tumor, but a film of the shoulder showed a half-moon shadow that suggested tumor, and a chest plate was obtained.

DR. MICHELSEN: The description of pain suggests involvement of the sixth and seventh nerve roots on the right.

DR. SWEET: What sort of lesion would explain that?

DR. MICHELSEN: I am not prepared to say. I am just suggesting that the distribution of the pain sounds more like root than peripheral pain.

DR. SWEET: Do you think it likely to be caused by a tumor in the chest?

DR. MICHELSEN: No; that is why I asked if x-ray films of the cervical spine had been taken.

DR. SWEET: I do not believe that the symptoms, other than the cough, were caused by the tumor.

I do not recall what I put down as my preoperative diagnosis, but Dr. Robbins and I finally concluded that it was a cyst of some kind. We considered neurofibroma.

It turned out to be a solid tumor but one of soft consistence. The x-ray films had localized it exactly; it was adherent to the trachea and had to be separated from the esophagus. Only a portion of the tumor was between the two organs, the majority of it protruding into the right side of the chest posteriorly, not anteriorly. As I freed it from its pleural covering and dissected it free, it looked like a goiter. As I followed it up I could see that its real attachments, as judged by vascular connections, were coming from the neck. I finally developed it down to a rather broad pedicle, which was obviously the lower pole of the thyroid gland, not a substernal goiter but a posterior mediastinal one. There was no evidence of goiter in the neck. The mass was so large that it could not have been removed from above.

CLINICAL DIAGNOSIS

Mediastinal cyst.

DR. HARWOOD'S DIAGNOSIS

Tracheal cyst (? bronchiogenic).

ANATOMICAL DIAGNOSIS

Colloid goiter.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Microscopic sections confirmed the diagnosis of colloid goiter.

DR. WILLIAM B. BREED: How do you explain the symptoms?

DR. SWEET: I do not. The only symptom that the tumor caused was the cough.

DR. MICHELSEN: What about the pain? Did it continue to bother him?

DR. SWEET: At the time of discharge, the patient said that it was improved, but not completely.

It was my impression that the pain was due to a bursitis or to a cervical arthritis or something of that sort. At a subsequent follow-up visit, however, he was in an excellent state of health. Although there was still a certain amount of stiffness of the arm at the shoulder, he was completely relieved of pain.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established in 1828

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Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

STREPTOCOCCUS SORE THROATS AND SCARLET FEVER

During World War I many studies of scarlet fever and other streptococcal infections were made in the United States Army camps. Considerable information was acquired concerning the significance of these infections and their mode of spread. Since that time, the general use of the Dick test as a measure of susceptibility to scarlet fever and the classification of streptococci into specific groups and types have made possible more intelligent and more precise epidemiologic studies, and have served to clarify the relation between scarlet fever and other hemolytic streptococcus infections of the upper respiratory tract. The application of this knowledge to recent studies of scarlet-fever outbreaks in Army camps has thrown further light on this important subject. This, in turn, has served to bring into focus certain inconsistencies in the public-health attitude toward these infections, which deserve reconsideration in the light of present-day knowledge.

Schwentker,[1] in a recent report of a commission established by the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, presented a survey of hemolytic streptococci in certain Army camps. At three of the posts in which the commission's investigation was carried out there were only sporadic cases of scarlet fever, but at another post an epidemic of this disease occurred. The results of these studies are of interest and serve to corroborate the impressions gained in many other similar studies carried out in this country and in England and Germany since the introduction of the serologic classification of streptococci into Griffith's agglutinative types.

Briefly, Schwentker and the other members of the commission concluded from their studies that during an epidemic of scarlet fever most of the cases are caused by a single type of streptococcus. This type also represents a high percentage of the strains recovered from normal carriers. During endemic periods, on the other hand, no single strain predominates among the streptococci causing scarlet fever, a number of types usually being involved. These types are also found in normal carriers but they do not predominate over the other nonscarlatinal strains. They also found a definite relation between the gross streptococcus-carrier rate and the incidence of scarlet fever. The same relation held for the Group A (human virulent) streptococcus-carrier rate, as well as the carrier rate for the scarlatinal types. The changes in the gross carrier rate were due primarily to variations in the carrier rate of virulent Group A strains, and these in turn depended on changes in the rate for the carriers of the scarlatinal type.

During an outbreak of scarlet fever in a given ward these investigators found that the scarlatinal

strain of streptococcus becomes distributed throughout the occupants of the ward to a varying degree. Depending on the degree of this distribution, it fails to reach a certain proportion of the men and they naturally remain well. Among those who come in contact with the scarlatinal strain some are resistant to the organism, presumably because of an antibacterial immunity. Regardless of their Dick reactions they remain well, and either promptly eliminate the streptococcus or become carriers. Those without bacterial immunity develop evidence of clinical infection. The Dick-positive patients, that is, those who are susceptible to the toxin, develop scarlet fever, whereas those who are Dick negative have streptococcal tonsillitis without a rash.

A second clinical and epidemiologic study of an explosive outbreak of streptococcal sore throat in an army camp was recently reported by Bloomfield and Rantz.[2] A total of 341 cases occurred within a period of five days, and about 83 per cent of them began in the first two days. In approximately one fourth of all these cases there was a classic scarlatinal rash, which ran the usual course with eventual desquamation. In other patients there was only a trace of exanthem, and in the majority a rash was not seen at any time. However, there was no clinical indication that the patients with a rash were suffering from a disease that was in any other way different from that of the men without a rash.

These workers raise the question whether the use of the term "scarlet fever" with the implication of its fundamental difference from "acute tonsillitis" does not serve to maintain confusion and diagnostic quibbling. They believe that the entire group should be referred to as streptococcal sore throat (with or without associated scarlatinal rash). They also think that the same rules for isolation and quarantine should hold for all these cases, regardless of whether or not a rash occurs.

At the present time health departments throughout the country quarantine "scarlet fever" but not "tonsillitis," and this, according to Bloomfield and Rantz, shows a complete misunderstanding of the subject. In Massachusetts and in many other states not only does this incongruity persist, but there are differences in the isolation and quarantine periods within adjacent subdivisions of the same state. It would be well for the state and local health departments to reconsider this problem at the present time with a view to bringing their regulations in accord with present knowledge concerning this group of infections, and take the same opportunity to standardize isolation and quarantine regulations.

References

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HIERONYMUS FABRICIUS

Fabricius is best known as the teacher of Harvey. About 1600, Harvey attended the medical school at Padua, where Fabricius taught anatomy. It was there, in the old anatomical amphitheatre, which is still in existence, that Harvey heard for the first time, when attending one of the candlelight lectures of this famous teacher, a description of the valves of the veins. Fabricius was the first to demonstrate them publicly, and there seems to be little reason to doubt the inspiration Harvey received, to use Osler's phrase, from "the most distinguished teacher of the time, in the most distinguished school of Europe." The anatomical description and the function of the veins, as disclosed in Fabricius's lectures, stimulated Harvey to discover the circulation of the blood. He received at the same time an impetus to study embryology, a subject later to be markedly influenced by one of his books.

Two treatises by Fabricius, one on the formation of the egg and of the chick and the other on the formed fetus, have long remained buried in "that most excellent preservative, the Latin language." Dr. Howard B. Adelmann,* professor of histology

**The Embryological Treatises of Hieronymus Fabricius of Aquapendente: The formation of the egg and of the chick (De Formatione Ovi et Pulli) and the formed fetus (De Formato Foetu).* A facsimile edition, with an introduction, a translation and a commentary by Howard B. Adelmann, Ph.D. 883 pp. Ithaca, New York: Cornell University Press, 1942.

and embryology at Cornell University, has translated these into English, with the addition of a brief biography of Fabricius, an essay on embryology before the time of this great anatomist, an analysis of the treatises and a bibliography of the known editions. The translations are given in full, and facsimiles of each work are reproduced; there are numerous notes and commentaries, a list of references and an excellent index. This publication is one of the recent outstanding scholarly productions in the history of medicine. Furthermore, the book, published by the Cornell University Press, is a superb example of the work of a modern press.

Fabricius's position in embryology is not particularly easy to assess. It is correct to refer to him as the most distinguished teacher of his time, and as Adelmann has pointed out, the embryologic treatises represent no mean achievement. In fact, some believe that they are of even greater anatomical importance than his work on the valves of the veins.

Fabricius lacked, as did most of his contemporaries, what Singer has called "complete speculative freedom." Needham was, moreover, impressed by Fabricius's "genius for exsuccous and formal discussions." Osler wondered how Fabricius, a teacher of wide learning and remarkable powers of observations, "could have been so blinded as to overlook the truth which was tumbling out, so to speak, at his feet." Dr. Adelmann believes that Fabricius's faults, particularly his subservience to authority, were probably unavoidable—"a fault Fabricius shared, not only with Vesalius who preceded him, but also with many who came after, even Harvey. He adds: "The basic explanation, moreover, is not far to seek. We are all children of our times; we all see with the eyes of the centuries that have preceded us; truth dawns but slowly on the human mind."

MEDICAL EPONYM

Gradenigo's Syndrome

Giuseppe Gradenigo (1859–1926), professor of ophthalmology at Turin, published a paper entitled "Über circumscripte Leptomeningitis mit spinalen Symptomen und über Paralyse des N. abducens otitischen Ursprungs [Circumscribed Leptomeningitis with Spinal Symptoms and Paralysis of the N. abducens of Otitic Origin]," which appeared in the *Archiv für Ohrenheilkunde* (62: 255–270, 1904). A portion of the translation follows:

> There exists a peculiar symptom complex in the association of acute otitis media (with or without reactive mastoiditis) and isolated paresis or paralysis of the N. abducens on the side corresponding to the aural lesion, and without the occurrence of other local or general signs of disease. . . . The syndrome under discussion is characterized chiefly by three symptoms, which are intimately related to one another and which ordinarily are complained of by the patient himself: acute inflammation of the middle ear, persistent pains in the temporal and parietal region and paralysis of the N. abducens.

R. W. B.

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DEATHS

DASCOMBE — OTHO L. DASCOMBE, M.D., of Waltham, died September 26. He was in his sixty-fourth year.

Dr. Dascombe received his degree from Johns Hopkins University School of Medicine, in 1905. Following internship at Waltham Hospital, he was appointed a staff member in 1918. He was a fellow of the Massachusetts Medical Society and a member of the American Medical Association.

A sister and a brother survive.

LELAND — GEORGE A. LELAND, JR., M.D., of Brookline, died September 22. He was in his fifty-eighth year.

Dr. Leland received his degree from Harvard Medical School in 1911. He then became house officer at the Massachusetts General Hospital and was associate surgeon there at the time of his death. He was a member of the staff of the Collis P. Huntington Memorial Hospital, associate surgeon of the Palmer Memorial Hospital, consulting surgeon of the Massachusetts Eye and Ear Infirmary and of the Addison Gilbert Hospital in Gloucester and a member of the staff of the New Hampshire Memorial Hospital at Concord. He had been instructor for fifteen years at Harvard Medical School.

He was a member of the Massachusetts Medical Society, the American Medical Association, the American Surgical Association, the American College of Surgeons, the New England Surgical Society, the New England Cancer Society and the New England Obstetrical and Gynecological Society.

His widow, his mother and a daughter survive.

BOOK REVIEW

Renal Lithiasis. By Charles C. Higgins, M.D. 12°, cloth, 140 pp., with 18 illustrations. Springfield, Illinois: Charles C Thomas, 1943. $3.00.

This short monograph is based on the Beaumont Lectures on Renal Lithiasis, delivered by the author. More than half the book deals with a discussion of the etiology of renal stone and of its relation to faulty diet and vitamin A deficiency. Included in this chapter is the technic of stone analysis. This is followed by a brief review of the surgical management of cases of renal stone. A short chapter on the dietary treatment and prevention of kidney stones, with a list of sample diets, concludes the book.

The book is far too elementary to be of value to the established urologist. The chapter on surgical management is sketchy, and the discussion on the dietary treatment and prevention of kidney stones will remind the average surgeon of the limited success he has had with this form of therapy.

From the student's point of view, the survey of the literature on the etiology of renal lithiasis suffers by being far too biased in favor of dietary imbalance and vitamin A deficiency as the main causes of renal stone. There are many significant papers that point to the incompleteness of the evidence for such a concept of stone formation in the experimental animal, and the relation of diet to the formation of renal stones in man is even more tenuously established.

(Notices on page x)